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(54) **ANTIBODY SPECIFIC FOR MUTANT PRESENILIN 1**

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(60) Continuation of application No. 09/689,159, filed on Oct. 12, 2000, now Pat. No. 6,998,467, which is a division of application No. 08/509,359, filed on Jul. 31, 1995, now abandoned, which is a continuation-in-part of application No. 08/496,841, filed on Jun. 28, 1995, now Pat. No. 6,210,919, which is a continuation-in-part of application No. 08/431,048, filed on Apr. 28, 1995, now Pat. No. 6,531,586.

(51) **Int. Cl.**
C07K 16/28 (2006.01)

(52) **U.S. Cl.** **530/388.1**; 530/389.1; 530/809

(58) **Field of Classification Search** ..... None
See application file for complete search history.

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(57) **ABSTRACT**

The present invention describes the identification, isolation, cloning, and determination of the Alzheimer Related Membrane Protein (ARMP) gene on chromosome 14 and a related gene, E5-1, on chromosome 1. Normal and mutant copies of both genes are presented. Transcripts and products of these genes are useful in detecting and diagnosing Alzheimer's disease, developing therapeutics for treatment of Alzheimer's disease, as well as the isolation and manufacture of the protein and the construction of transgenic animals expressing the mutant genes.

14 Claims, 10 Drawing Sheets

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FIG. 1A

FIG. 1B

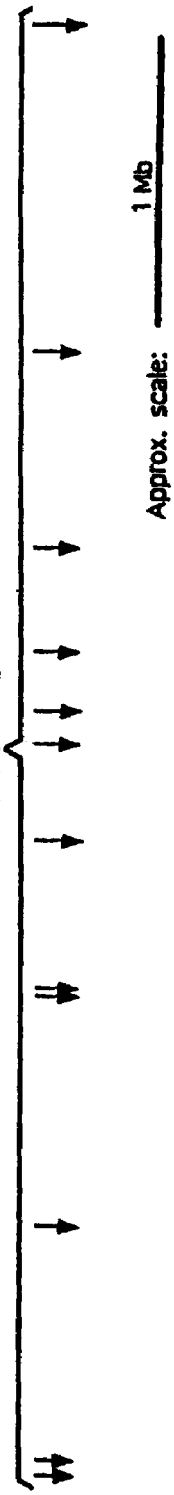
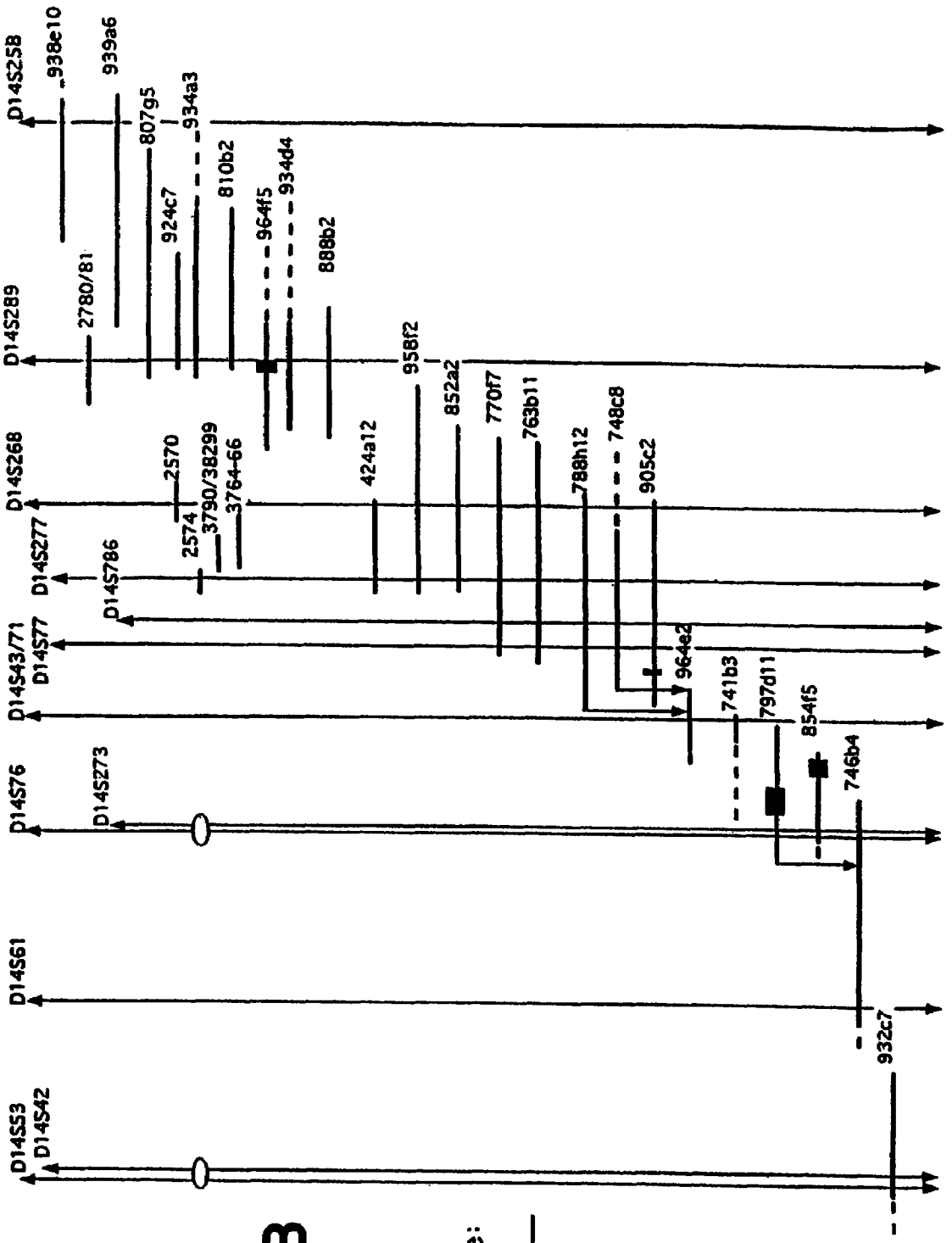


FIG. 1C

FIG. 1D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958f2
852a2
770f7
763b11
748c8
D14S268
2570
424a12
788h12
905c2
D14S277
2574
3790/38299
3764-66
D14S786
D14S43/71
D14S77
964e2
741b3
797d11
854f5
D14S76
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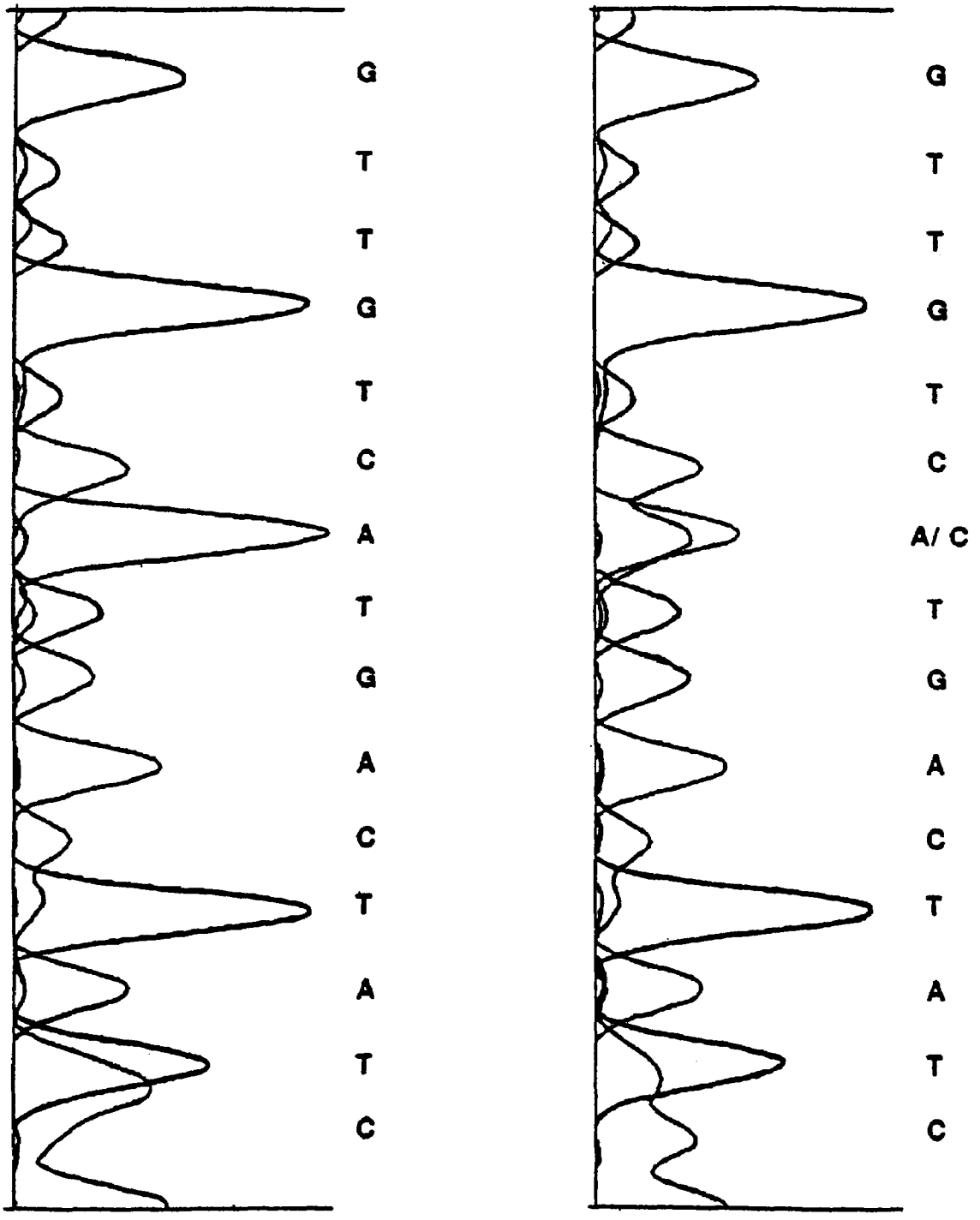
D14S42
Approx. Scale:
1 Mb

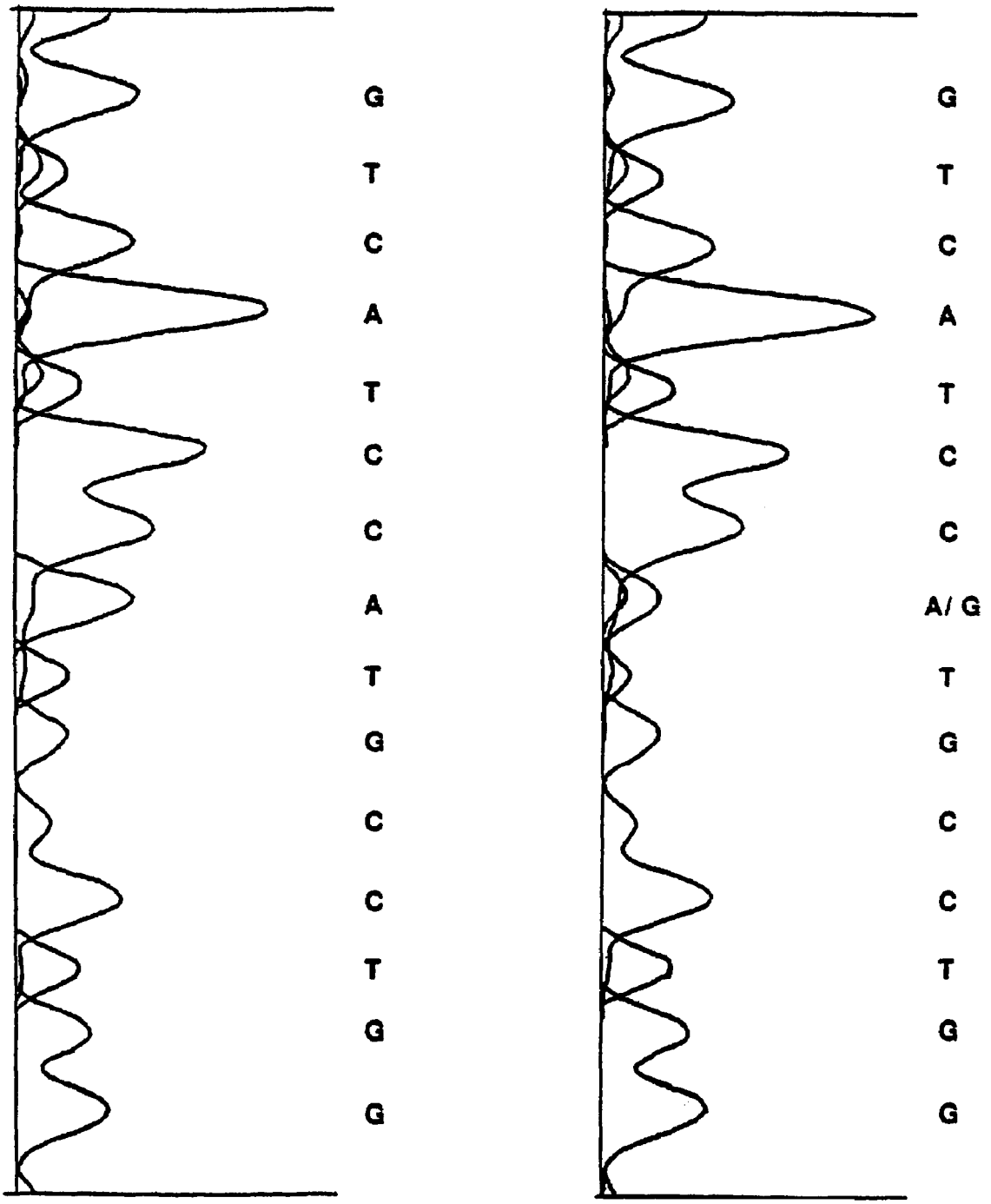
FIG. 1B

FIG. 2A



Met 146 Leu

FIG. 2B



His 163 Arg

FIG. 2C

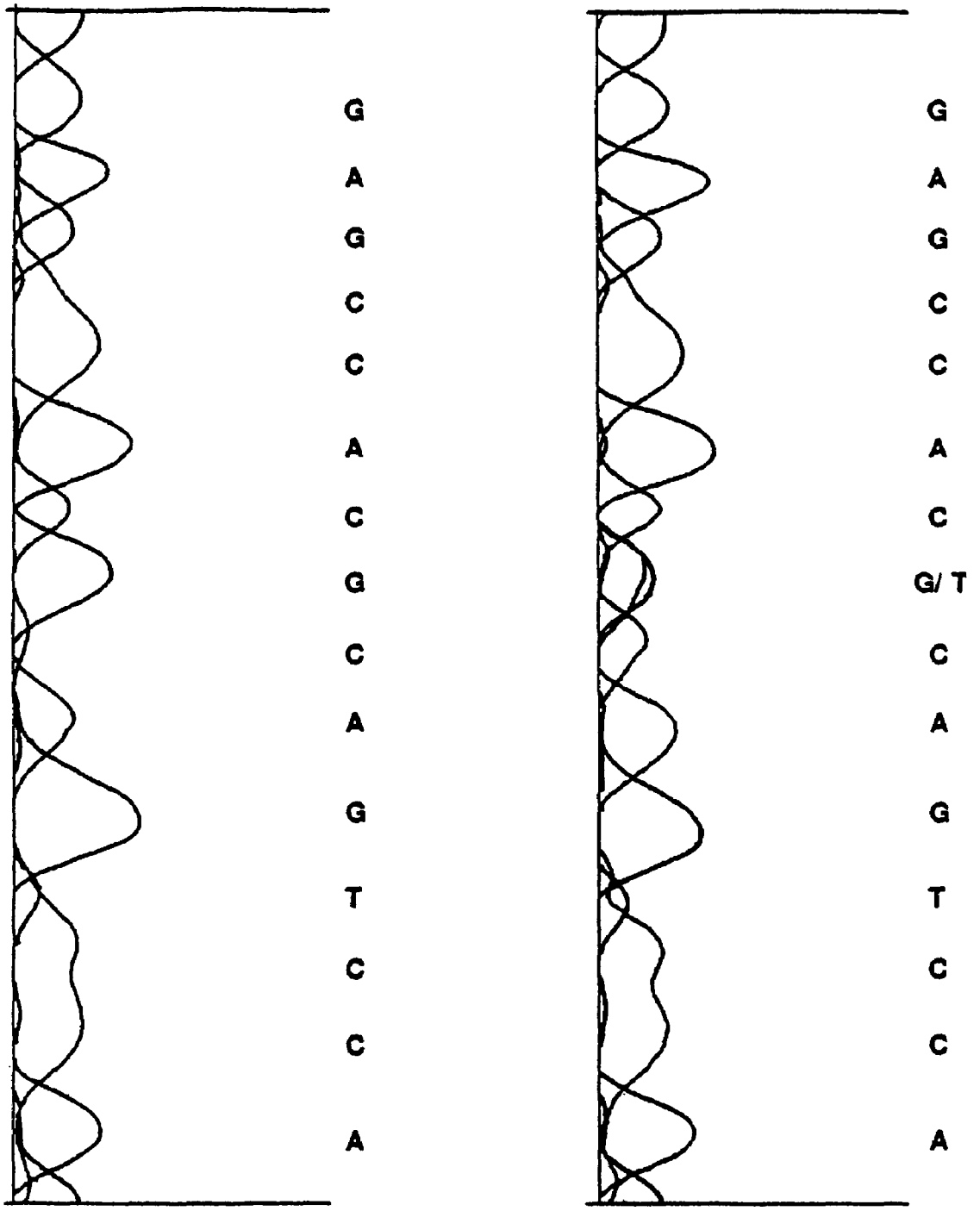


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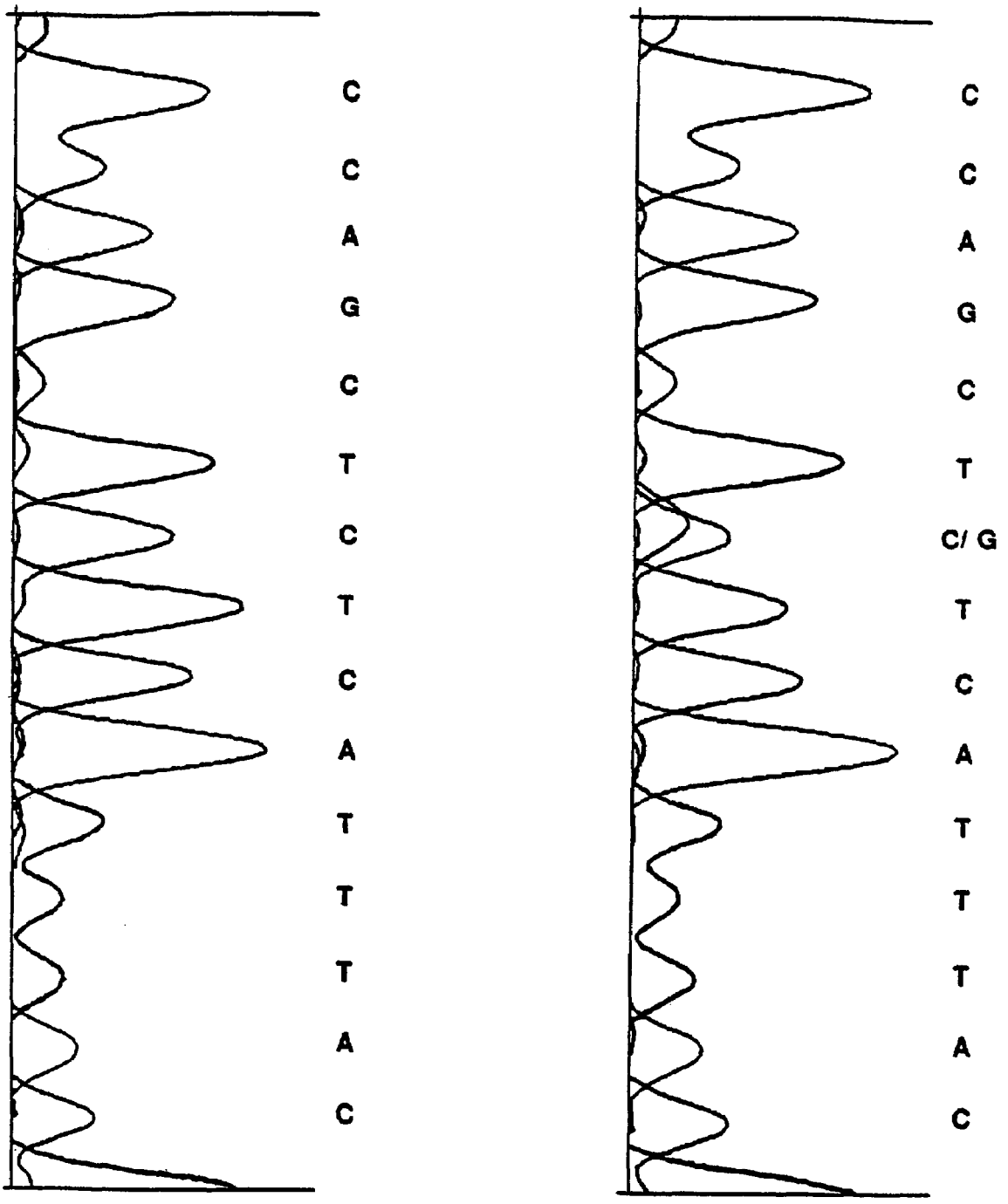
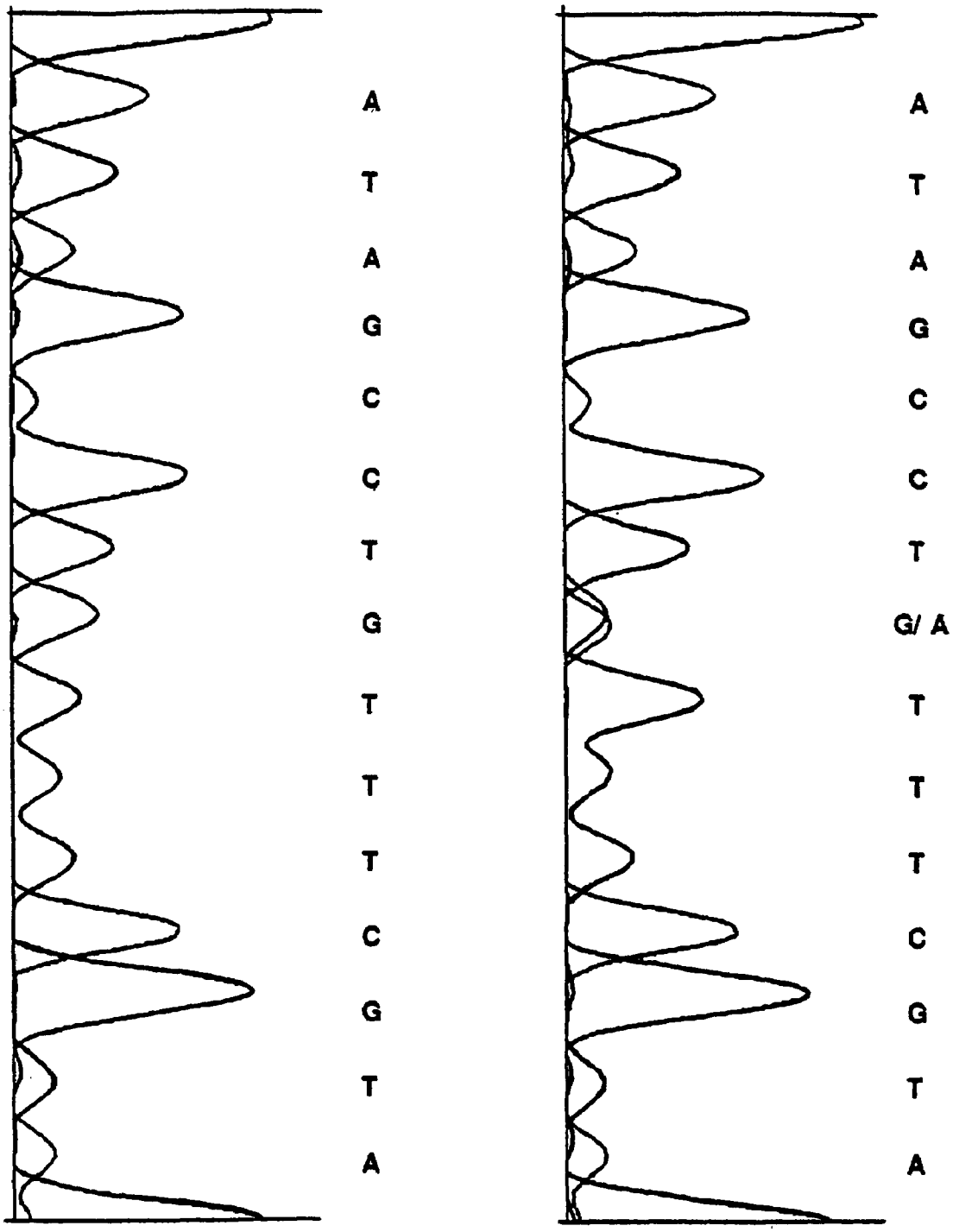
FIG. 2D



Leu 286 Val

FIG. 2E



Cys 410 Tyr

FIG. 3A

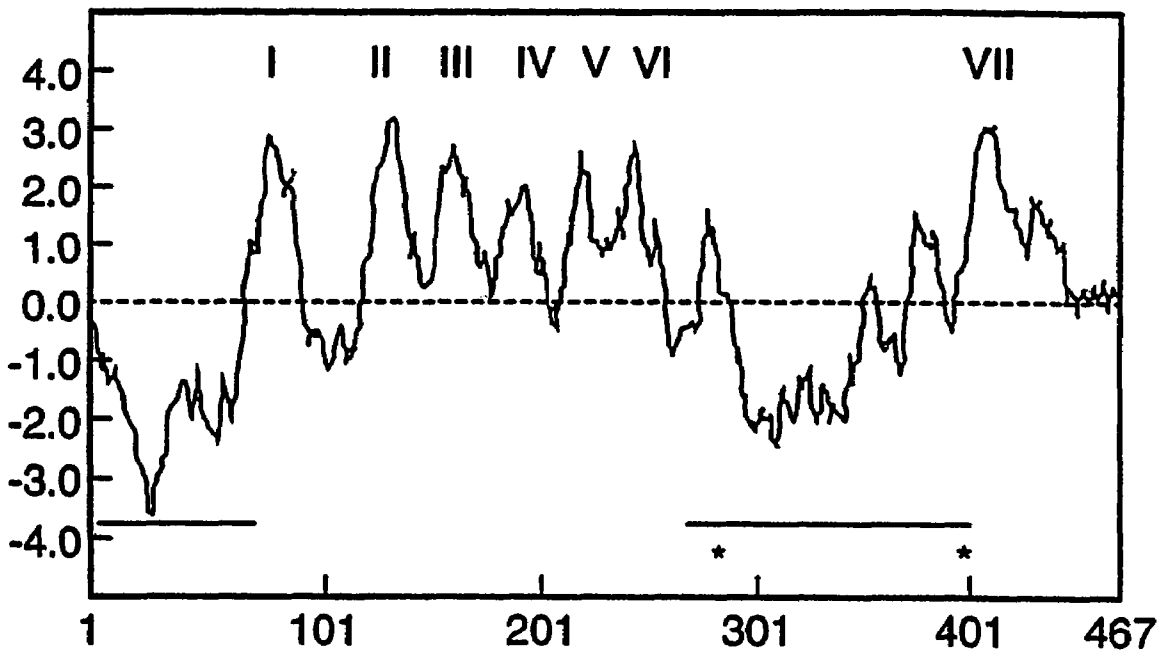
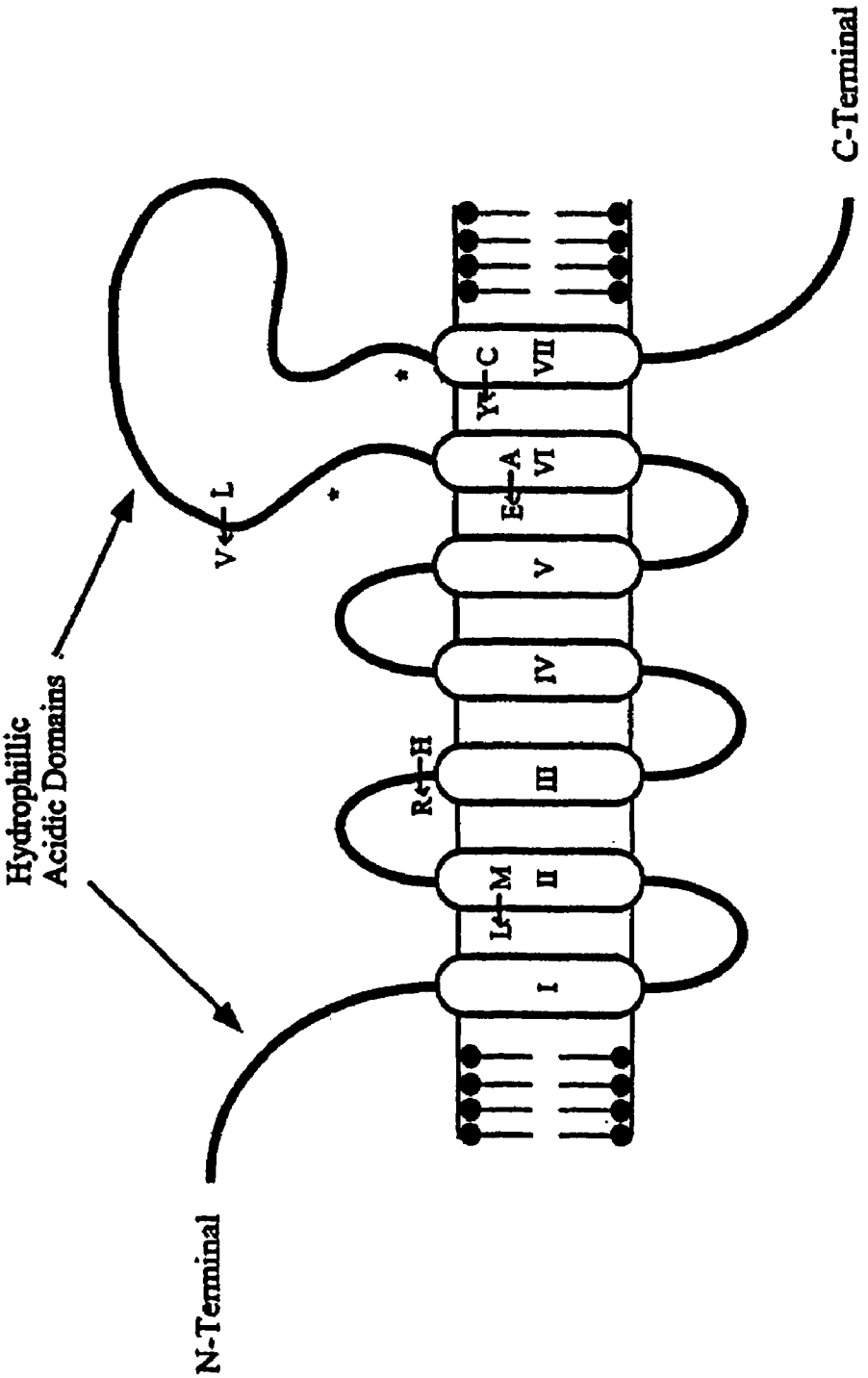


FIG. 3B


Hydrophillic
Acidic Domains
N-Terminal
C-Terminal
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II
III
IV
V
VI
VII
L
M
R
H
E
A
Y
C
V
L

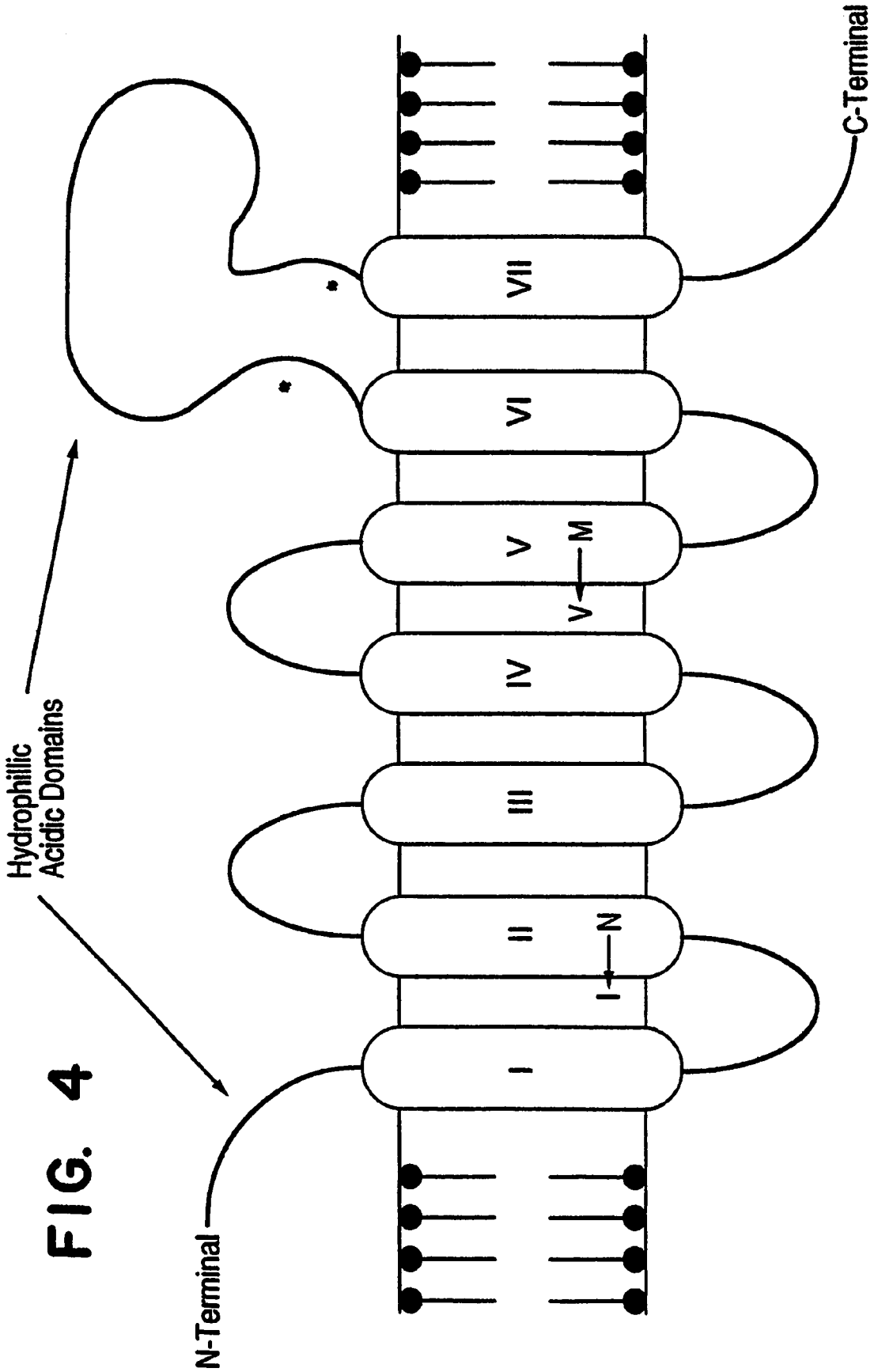
C-Terminal
VII
VI
V
M
V
IV
III
II
N
I
I
Hydrophilic
Acidic Domains
N-Terminal

FIG. 4

ANTIBODY SPECIFIC FOR MUTANT PRESENILIN 1

RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 09/689,159, filed Oct. 12, 2000, now U.S. Pat. No. 6,998,467 which is a divisional of U.S. patent application Ser. No. 08/509,359, filed Jul. 31, 1995, now Abandoned, which is a continuation-in-part of U.S. patent application Ser. No. 08/496,841, now U.S. Pat. No. 6,210,919, filed Jun. 28, 1995, which is a continuation-in-part of U.S. patent application Ser. No. 08/431,048, now U.S. Pat. No. 6,531,586, filed Apr. 28, 1995.

FIELD OF THE INVENTION

The present invention relates generally to the field of neurological and physiological dysfunctions associated with Alzheimer's Disease. More particularly, the invention is concerned with the identification, isolation and cloning of the gene which when mutated is associated with Alzheimer's Disease as well as its transcript, gene products and associated sequence information and neighbouring genes. The present invention also relates to methods of diagnosing for and detection of carriers of the gene, Alzheimer's Disease diagnosis, gene therapy using recombinant technologies and therapy using the information derived from the DNA, protein, and the metabolic function of the protein.

BACKGROUND OF THE INVENTION

In order to facilitate reference to various journal articles, a listing of the articles is provided at the end of this specification.

Alzheimer's Disease (AD) is a degenerative disorder of the human central nervous system characterized by progressive memory impairment and cognitive and intellectual decline during mid to late adult life (Katzman, 1986). The disease is accompanied by a constellation of neuropathologic features principal amongst which are the presence of extracellular amlyoid or senile plaques and the neurofibrillary degeneration of neurons. The etiology of this disease is complex, although in some families it appears to be inherited as an autosomal dominant trait. However, even among these inherited forms of AD, there are at least three different genes which confer inherited susceptibility to this disease (St. George-Hyslop et al., 1990). The $_e$4 (Cys112Arg) allelic polymorphism of the Apolipoprotein E (AopE) gene has been associated with AD in a significant proportion of cases with onset late in life (Saunders et al., 1993; Strittmatter et al., 1993). Similarly, a very small proportion of familial cases with onset before age 65 years have been associated with mutations in the β-amyloid precursor protein (APP) gene (Chartier-Harlin et al., 1991; Goate et al., 1991; Murrell et al., 1991; Karlinsky et al., 1992; Mullan et al., 1992). A third locus (AD3) associated with a larger proportion of cases with early onset AD has recently been mapped to chromosome 14q24.3 (Schellenberg et al., 1992; St. George-Hyslop et al., 1992; Van Broeckhoven et al., 1992).

Although chromosome 14q carries several genes which could be regarded as candidate genes for the site of mutations associated with AD3 (e.g. cFOS, alpha-1-antichymotrypsin, and cathepsin G), most of these candidate genes have been excluded on the basis of their physical location outside the AD3 region and/or the absence of mutations in their respective open reading frames (Schellenberg, G D et al., 1992; Van Broeckhoven, C et al., 1992; Rogaev et al., 1993; Wong et al., 1993).

There have been several developments and commercial directions in respect of treatment of Alzheimer's disease and diagnosis thereof. Published PCT application WO 94 23049 describes transfection of high molecular weight YAC DNA into specific mouse cells. This method is used to analyze large gene complexes, for example the transgenic mice may have increased amyloid precursor protein gene dosage, which mimics the trisomic condition that prevails in Downs Syndrome and the generation of animal models with β-amyloidosis prevalent in individuals with Alzheimer's Disease. Published international application WO 94 00569 describes transgenic non-human animals harbouring large trans genes such as the trans gene comprising a human amyloid precursor protein gene. Such animal models can provide useful models of human genetic diseases such as Alzheimer's Disease.

Canadian Patent application 2096911 describes a nucleic acid coding for amyloid precursor protein-cleaving protease, which is associated with Alzheimer's Disease and Down's syndrome. The genetic information may be used to diagnose Alzheimer's disease. The genetic information was isolated from chromosome 19. Canadian patent application 2071105, describes detection and treatment of inherited or acquired Alzheimer's disease by the use of YAC nucleotide sequences. The YACs are identified by the numbers 23CB10, 28CA12 and 26FF3.

U.S. Pat. No. 5,297,562, describes detection of Alzheimer's Disease having two or more copies of chromosome 21. Treatment involves methods for reducing the proliferation of chromosome 21 trisomy. Canadian Patent Application 2054302, describes monoclonal antibodies which recognize human brain cell nucleus protein encoded by chromosome 21 and are used to detect changes or expression due to Alzheimer's Disease or Down's Syndrome. The monoclonal antibody is specific to a protein encoded by human chromosome 21 and is linked to large pyramidal cells of human brain tissue.

By extensive effort and a unique approach to investigating the AD3 region of chromosome 14q, the Alzheimer's related membrane protein (ARMP) gene has been isolated, cloned and sequenced from within the AD3 region on chromosome 14q24.3. In addition, direct sequencing of RT-PCR products spanning this 3.0 kb cDNA transcript isolated from affected members of at least eight large pedigrees linked to chromosome 14, has led to the discovery of missence mutations in each of these different pedigrees. These mutations are absent in normal chromosomes. It has not been established that the ARMP gene is causative of familial Alzheimer's Disease type AD3. In realizing this link, it is understood that mutations in this gene can be associated with other cognitive, intellectual, or psychological disease such as cerebral hemorrhage, schizophrenia, depression, mental retardation and epilepsy. These phenotypes are present in these AD families and these phenotypes have been seen in mutations of the APP protein gene. The Amyloid Precursor Protein (APP) gene is also associated with inherited Alzheimer's Disease. The identification of both normal and mutant forms of the ARMP gene and gene products has allowed for the development of screening and diagnostic tests for ARMP utilizing nucleic acid probes and antibodies to the gene product. Through interaction with the defective gene product and the pathway in which

this gene product is involved, gene therapy, manipulation and delivery are now made possible.

SUMMARY OF THE INVENTION

Various aspects of the invention are summarized as follows. In accordance with a first aspect of the invention, a purified mammalian polynucleotide is provided which codes for Alzheimer's related membrane protein (ARMP). The polynucleotide has a sequence which is the functional equivalent of the DNA sequence of ATCC deposit 97124, deposited Apr. 28, 1995. The mammalian polynucleotide may be in the form of DNA, genomic DNA, cDNA, mRNA and various fragments and portions of the gene sequence encoding ARMP. The mammalian DNA is conserved in many species, including human and rodents, example, mice. The mouse sequence encoding ARMP has greater than 95% homology with the human sequence encoding the same protein.

Purified human nucleotide sequences which encode mutant ARMP have mutations at nucleotide position i) 685, A→C ii) 737, A→G iii) 986, C→A, iv) 1105, C→G, v) 1478, G→A, vi) 1027, C→T, vii) 1102, C→T and viii) 1422, C→G of Sequence ID No: 1 as well as in the cDNA sequence of a further human clone of a sequence identified by ID NO:133.

The nucleotide sequences encoding ARMP have an alternative splice form in the genes open reading frame. The human cDNA sequence which codes for ARMP has sequence ID No. 1 as well as sequence SEQ ID NO:133 as sequenced in another human clone. The mouse sequence which encodes ARMP has SEQ ID NO:3, as well as SEQ ID NO:135 derived from a further clone containing the entire coding region. Various DNA and RNA probes and primers may be made from appropriate polynucleotide lengths selected from the sequences. Portions of the sequence also encode antigenic determinants of the ARMP.

Suitable expression vectors comprising the nucleotide sequences are provided along with suitable host cells transfected with such expression vectors.

In accordance with another aspect of the invention, purified mammalian Alzheimer's related membrane protein is provided. The purified protein has an amino acid sequence encoded by polynucleotide sequence as identified above which for the human is SEQ ID NO: 2 and SEQ ID NO: 134 (derived from another clone). The mouse amino acid sequence is defined by SEQ ID NO: 4 and SEQ ID NO: 136, the later being translated from another clone containing the entire coding region. The purified protein may have substitution mutations selected from the group consisting of positions identified in SEQ ID NO: 2 and Sequence ID NO: 134.

i) M 146L
ii) H 163R
iii) A 246E
iv) L 286V
v) C 410 Y
vi) A 260 V
vii) A 285 V
viii) L 392 V

In accordance with another aspect of the invention, are polyclonal antibodies raised to specific predicted sequences of the ARMP protein. Polypeptides of at least six amino acid residues are provided. The polypeptides of six or greater amino acid residues may define antigenic epitopes of the ARMP. Monoclonal antibodies having suitably specific binding affinity for the antigenic regions of the ARMP are prepared by use of corresponding hybridoma cell lines. In addition, other polyclonal antibodies may be prepared by inoculation of animals with suitable peptides or holoprotein which add suitable specific binding affinities for antigenic regions of the ARMP.

In accordance with another aspect of the invention, an isolated DNA molecule is provided which codes for E5-1 protein. A plasmid including this nucleic acid was deposited with the ATCC under the terms of the Budapest Treaty on Jun. 28, 1995 and has been assigned ATCC accession number 97214.

In accordance with another aspect of the invention, purified E5-1 protein is provided, having amino acid SEQ ID NO:138.

In accordance with another aspect of the invention a bioassay is provided for determining if a subject has a normal or mutant ARMP, where the bioassay comprises:

providing a biological sample from the subject

conducting a biological assay on the sample to detect a normal or mutant gene sequence coding form ARMP, a normal or mutant ARMP amino acid sequence, or a normal or defective protein function.

In accordance with another aspect of the invention, a process is provided for producing ARMP comprising culturing one of the above described transfected host cells under suitable conditions, to produce the ARMP by expressing the DNA sequence. Alternatively, ARMP may be isolated from mammalian cells in which the ARMP is normally expressed.

In accordance with another aspect of the invention, is a therapeutic composition comprising ARMP and a pharmaceutically acceptable carrier.

In accordance with another aspect of the invention, a recombinant vector for transforming a mammalian tissue cell to express therapeutically effective amounts of ARMP in the cells is provided. The vector is normally delivered to the cells by a suitable vehicle. Suitable vehicles include vaccinia virus, adenovirus, adeno associated virus, retrovirus, liposome transport, neuraltripic viruses, Herpes simplex virus and other vector systems.

In accordance with another aspect of the invention, a method of treating a patient deficient in normal ARMP comprising administering to the patient a therapeutically effective amount of the protein targeted at a variety of patient cells which normally express ARMP. The extent of administration of normal ARMP being sufficient to override any effect the presence of the mutant ARMP may have on the patient. As an alternative to protein, suitable ligands and therapeutic agents such as small molecules and other drug agents may be suitable for drug therapy designed to replace the protein and defective ARMP, displace mutant ARMP, or to suppress its formation.

In accordance with another aspect of the invention an immuno therapy for treating a patient having Alzheimer's Disease comprises treating the patient with antibodies specific to the mutant ARMP to reduce biological levels or activity of the mutant ARMP in the patient. To facilitate such amino acid therapy, a vaccine composition may be provided for evoking an immune response in a patient of Alzheimer's disease where the composition comprises a mutant ARMP and a pharmaceutically acceptable carrier with or without a suitable excipient. The antibodies developed specific to the mutant ARMP could be used to target appropriately encapsulated drugs/molecules, specific cellular/tissue sites. Therapies utilizing specific ligands which bind to normal or wild type ARMP of either mutant or wild type and which augments normal function of ARMP in membranes and/or cells or inhibits the deleterious effect of the mutant protein are also made possible.

In accordance with another aspect of the invention, a transgenic animal model for Alzheimer's Disease which has the

mammalian polynucleotide sequence with at least one mutation which when expressed results in mutant ARMP in animal cells and thereby manifests a phenotype. For example, the human Prion gene when overexpressed in rodent peripheral nervous system and muscle cells causes a quite different response in the animal than the human. The animal may be a rodent and is preferably a mouse, but may also be other animals including rat, pig, *Irosophila melanogaster, C. elegans* (nematode), all of which are used for transgenic models. Yeast cells can also be used in which the ARMP Sequence is expressed from an artificial vector.

In accordance with another aspect of the invention, a transgenic mouse model for Alzheimer's Disease has the mouse gene encoding ARMP human or murine homologues mutated to manifest the symptoms. The transgenic mouse may exhibit symptoms of cognitive memory or behavioral disturbances. In addition or alternatively, the symptoms may appear as another cellular tissue disorder such as in mouse liver, kidney, spleen or bone marrow or other organs in which the ARMP gene is normally expressed.

In accordance with another aspect of the invention, the protein can be used as a starting point for rationale drug design to provide ligands, therapeutic drugs or other types of small chemical molecules.

BRIEF DESCRIPTION OF THE DRAWINGS

Various aspects of the invention are described hereinafter with respect to the drawings wherein:

FIG. **1***a*. Genomic physical and transcriptional map of the AD3 region of chromosome 14. Genetic map inter-marker genetic distances averaged for male and female meiosis are indicated in centiMorgans.

FIG. **1***b*. Is the constructed physical contig map of overlapping genomic DNA fragments cloned into YACs spanning a FAD locus on chromosome 14q.

FIG. **1***c*. Regions of interest within the constructed physical contig map.

FIG. **1***d*. Transcriptional map illustrating physical locations of the 19 independent longer cDNA clones.

FIG. **2**(*a*). Automated fluorescent chromatograms representing the change in nucleic acids which direct (by the codon) the amino acid sequence of the gene; Met 146 Leu.

FIG. **2**(*b*). Automated fluorescent chromatograms representing the change in nucleic acids which direct (by the codon) the amino acid sequence of the gene; His 163 Arg.

FIG. **2**(*c*). Automated fluorescent chromatograms representing the change in nucleic acids which direct (by the codon) the amino acid sequence of the gene; Ala 246 Glu.

FIG. **2**(*d*). Automated fluorescent chromatograms representing the change in nucleic acids which direct (by the codon) the amino acid sequence of the gene; Leu 286 Val.

FIG. **2**(*e*). Automated fluorescent chromatograms representing the change in nucleic acids which direct (by the codon) the amino acid sequence of the gene; Cys 410 Tyr.

FIG. **3***a*. Hydropathy plot of the putative ARMP protein.

FIG. **3***b*. A model for the structural organization of the putative ARMP protein. Roman numerals depict the transmembrane domains. Putative glycosylation sites are indicated as asterisks and most of the phosphorylation sites are located on the same membrane face as the two acidic hydrophillic loops. The MAP kinase site is present at residue 114 . FAD mutation sites are indicated by horizontal arrows.

FIG. **4** shows the predicted structure of the E5-1 protein.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

In order to facilitate review of the various embodiments of the invention and an understanding of various elements and constituents used in making the invention and using same, the following definition of terms used in the invention description is as follows:

Alzheimer Related Membrane Protein gene (ARMP gene)—the chromosome 14 gene which when mutated is associated with familial Alzheimer's Disease and/or other inheritable disease phenotypes (e.g., cerebral hemorrhage, mental retardation, schizophrenia, psychosis, and depression). This definition is understood to include the various sequence polymorphisms that exist, wherein nucleotide substitutions in the gene sequence do not affect the essential function of the gene product, as well as functional equivalents of the nucleotide sequences of SEQ ID NO:1, SEQ ID NO:133, SEQ ID NO:3 and SEQ ID NO:135. This term primarily relates to an isolated coding sequence, but can include some or all of the flanking regulatory elements and/or introns. The term ARMP gene includes the gene in other species analogous to the human gene which when mutated is associated with Alzheimer's Disease.

Alzheimer Related Membrane Protein (ARMP)—the protein encoded by the ARMP gene. The preferred source of protein is the mammalian protein as isolated from humans or animals. Alternatively, functionally equivalent proteins may exist in plants, insects and invertebrates (such as *C. elegans*). The protein may be produced by recombinant organisms, or chemically or enzymatically synthesized. This definition is understood to include functional variants such as the various polymorphic forms of the protein wherein amino acid substitutions or deletions within the amino acid sequence do not affect the essential functioning of the protein, or its structure. It also includes functional fragments of ARMP.

Mutant ARMP gene—The ARMP gene containing one or more mutations which lead to Alzheimer's Disease and/or other inheritable disease phenotypes (e.g., cerebral hemorrhage, mental retardation, schizophrenia, psychosis, and depression). This definition is understood to include the various mutations that exist, wherein nucleotide substitutions in the gene sequence affect the essential function of the gene product, as well as mutations of functional equivalents of the nucleotide sequences of SEQ ID NO:1, SEQ ID NO:133, SEQ ID NO:3 and SEQ ID NO:135 (the corresponding amino acid sequences). This term primarily relates to an isolated coding sequence, but also can include some or all of the flanking regulatory elements and/or introns.

Mutant ARMP—a mammalian protein that is highly analogous to ARMP in terms of primary structure, but wherein one or more amino acid deletions and/or substitutions result in impairment of its essential function, so that mammals, especially humans, whose ARMP producing cells express mutant ARMP rather than the normal ARMP, demonstrate the symptoms of Alzheimer's Disease and/or other relevant inheritable phenotypes (e.g. cerebral hemorrhage, mental retardation, schizophrenia, psychosis, and depression).

mARMP gene—mouse gene analogous to the human ARMP gene. Functional equivalent as used in describing gene sequences and amino acid sequences means that a recited sequence need not be identical to the definitive sequence of the Sequence ID Nos but need only provide a sequence which functions biologically and/or chemically the equivalent of the definitive sequence. Hence sequences which correspond to a definitive sequence may also be considered as functionally equivalent sequence.

mARMP—mouse Alzheimer related membrane protein, analogous to the human ARMP, encoded by the mARMP gene. This definition is understood to include the various polymorphic forms of the protein wherein amino acid substitutions or deletions of the sequence does not affect the essential functioning of the protein, or its structure.

Mutant mARMP—a mouse protein which is highly analogous to mARMP in terms of primary structure, but wherein one or more amino acid deletions and/or substitutions result in impairment of its essential function, so that mice, whose mARMP producing cells express mutant mARMP rather than the normal mARMP demonstrate the symptoms of Alzheimer's Disease and/or other relevant inheritable phenotypes, or other phenotypes and behaviours as manifested in mice.

ARMP carrier—a mammal in apparent good health whose chromosomes contain a mutant ARMP gene that may be transmitted to the offspring and who will develop Alzheimer's Disease in mid to late adult life.

Missense mutation—A mutation of nucleic acid sequence which alters a codon to that of another amino acid, causing an altered translation product to be made.

Pedigree—In human genetics, a diagram showing the ancestral relationships and transmission of genetic traits over several generations in a family.

E5-1 gene—the chromosome 1 gene which shows homology to the ARMP gene and which when mutated is associated with familial Alzheimer's Disease and/or other inheritable disease phenotypes. This definition is understood to include the various sequence polymorphisms that exist, wherein nucleotide substitutions in the gene sequence do not affect the essential function of the gene product, as well as functional equivalents of the nucleotide SEQ ID NO:137. This term also includes the gene in other species analogous to the human gene described herein.

E5-1 protein—the protein encoded by the E5-1 gene. This term includes the protein of SEQ ID NO:138 and also functional variants such as the various polymorphic and splice variant forms of the protein wherein amino acid substitutions or deletions within the amino acid sequence do not affect the essential functioning of the protein. The term also includes functional fragments of the protein.

Mutant E5-1 gene—the E5-1 gene containing one or more mutations which lead to Alzheimer's Disease. This term is understood to include the various mutations that exist, wherein nucleotide substitutions in the gene sequence affect the essential function of the gene product.

Mutant E5-1 protein—a protein analogous to E5-1 protein but wherein one or more amino acid deletions and/or substitutions result in impairment of its essential function such that mammals, especially humans, whose E5-1 producing cells express mutant E5-1 protein demonstrate the symptoms of Alzheimer's disease.

Linkage analysis—Analysis of co-segregation of a disease trait or disease gene with polymorphic genetic markers of defined chromosomal location.

hARMP gene—Human ARMP gene.

ORF—Open reading frame.

PCR—Polymerase chain reaction.

contig—continuous cloned regions.

YAC—yeast artificial chromosome.

RT-PCR—reverse transcription polymerase chain reaction.

SSR—Simple sequence repeat polymorphism.

The present invention is concerned with the identification and sequencing of the mammalian ARMP gene in order to gain insight into the cause and etiology of familial Alzheimer's Disease. From this information, screening methods and therapies for the diagnosis and treatment of the disease can be developed. The gene has been identified, cDNA isolated and cloned, its transcripts and gene products identified and sequenced. During such identification of the gene, considerable sequence information has also been developed on intron information in the ARMP gene, flanking untranslated information and signal information and information involving neighbouring genes in the AD3 chromosome region. Direct sequencing of overlapping RT-PCR products spanning the human gene isolated from affected members of large pedigrees linked to chromosome 14 has led to the discovery of missense mutation which co-segregate with the disease.

Although it is generally understood that Alzheimer's Disease is a neurological disorder, most likely in the brain, expression of ARMP has been found in varieties of human tissue such as heart, brain, placenta, lung, liver, skeletal muscle, kidney and pancreas. Although this gene is expressed widely, the clinically apparent phenotype exists in brain although it is conceivable that biochemical phenotypes may exist in these other tissues. As with other genetic diseases such as Huntington's Disease and APP—Alzheimer's, the clinical disease manifestation may reflect different biochemistries of different cell types and tissues (which stem from genetics and the protein). Such findings suggest that AD may not be solely a neurological disorder but may also be a systemic disorder, hence requiring alternative therapeutic strategies which may be targeted to other tissues or organs or generally in addition or separately from neuronal or brain tissues.

The ARMP mutations identified have been related to Alzheimer's Disease pathology. With the identification of sequencing of the gene and the gene product, probes and antibodies raised to the gene product can be used in a variety of hybridization and immunological assays to screen for and detect the presence of either a normal or mutated gene or gene product.

Patient therapy through removal or blocking of the mutant gene product, as well as supplementation with the normal. gene product by amplification, by genetic and recombinant techniques or by immunotherapy can now be achieved. Correction or modification of the defective gene product by protein treatment immunotherapy (using antibodies to the defective protein) or knock-out of the mutated gene is now also possible. Familial Alzheimer's Disease could also be controlled by gene therapy in which the gene defect is corrected in situ or by the use of recombinant or other vehicles to deliver a DNA sequence capable of expressing the normal gene product, or a deliberately mutated version of the gene product whose effect counter balances the deleterious consequences of the disease mutation to the affected cells of the patient.

The present invention is also concerned with the identification and sequencing of a second gene, the E5-1 gene on chromosome 1, which is associated with familial Alzheimer's Disease.

Disease mechanism insights and therapies analogous to those described above in relation to the ARMP gene will be available as a result of the identification and isolation of the E5-1 gene.

Isolating the Human ARMP Gene

Genetic Mapping of the AD3 Locus.

After the initial regional mapping of the AD3 gene locus to 14q24.3 near the anonymous microsatellite markers D14S43 and D14S53 (Schellenberg, G D et al., 1992; St. George-Hyslop, P et al., 1992; Van Broeckhoven, C et al., 1992), twenty one pedigrees were used to segregate AD as a putative autosomal dominant trait (St. George-Hyslop P et al., 1992)

and to investigate the segregation of 18 additional genetic markers from the 14q24.3 region which had been organized into a high density genetic linkage map (FIG. **1***b*) (Weissenbach et al., 1992; Gyapay et al., 1994). Pairwise maximum likelihood analyses previously published confirmed substantial cumulative evidence for linkage between FAD and all of these markers (Table 1). However, much of the genetic data supporting linkage to these markers were derived from six large early onset pedigrees FAD1 (Nee et al., 1983) FAD2 (Frommelt et al., 1991), FAD3 (Goudsmit et al., 1981; Pollen, 1993), FAD4 (Foncin et al., 1985) TOR1.1 (Bergamini, 1991) and 603 (Pericak-Vance et al., 1988) each of which provide at lease one anonymous genetic marker from 14q24.3 (St. George-Hyslop, P. et al., 1992).

In order to more precisely define the location of the AD3 gene relative to the known locations of the genetic markers from 14q24.3, recombinational landmarks were sought by direct inspection of the raw haplotype data only from genotyped affected members of the six pedigrees showing definitive linkage to chromosome 14. This selective strategy in this particular instance necessarily discards data from the reconstructed genotypes of deceased affected members as well as from elderly asymptomatic members of large pedigrees, and takes no account of the smaller pedigrees of uncertain linkage status. However, this strategy is very sound because it also avoids the acquisition of potentially misleading genotype data acquired either through errors in the reconstructed genotypes of deceased affected members arising from non-paternity or sampling errors or from the inclusion of unlinked pedigrees.

Upon inspection of the haplotype data for affected subjects, members of the six large pedigrees whose genotypes were directly determined revealed obligate recombinants at D14S48 and D14S53, and at D14S258 and D14S63. The single recombinant at D14S53, which depicts a telomeric boundary for the FAD region, occurred in the same AD affected subject of the FAD1 pedigree who had previously been found to be recombinant at several other markers located telomeric to D14S53 including D14S48 (St. George-Hyslop, P et al., 1992). Conversely, the single recombinant at D14S258, which marks a centromeric boundary of the FAD region, occurred in an affected member of the FAD3 pedigree who was also recombinant at several other markers centromeric to D14S258 including D14S63. Both recombinant subjects had unequivocal evidence of Alzheimer's Disease confirmed though standard clinical tests for the illness in other affected members of their families, and the genotypes of both recombinant subjects was informative and co-segregating at multiple loci within the interval centromeric to D14S53 and telomeric to D14S258.

When the haplotype analyses were enlarged to include the reconstructed genotypes of deceased affected members of the six large pedigrees as well as data from the remaining fifteen pedigrees with probabilities for linkage of less than 0.95, several additional recombinants were detected at one or more marker loci within the interval between D14S53 and D14S258. Thus, one additional recombinant was detected in the reconstructed genotype of a deceased affected member of each of three of the larger FAD pedigrees (FAD1, FAD2 and other related families), and eight additional recombinants were detected in affected members of five smaller FAD pedigrees. However, while some of these recombinants might have correctly placed the AD3 gene within a more defined target region, we were forced to regarded these potentially closer "internal recombinants" as unreliable not only of the reasons discussed earlier, but also because they provided mutually inconsistent locations for the AD3 gene within the D14S53-D14S258 interval.

Construction of a Physical Contig Spanning the AD3 Region.

As an initial step toward cloning the AD3 gene a contig of overlapping genomic DNA fragments cloned into yeast artificial chromosome vectors, phage artificial chromosome vectors and cosmid vectors was constructed (FIG. **1***b*). FISH mapping studies using cosmids derived from the YAC clones 932c7 and 964f5 suggested that the interval most likely to carry the AD3 gene was at least five megabases in size. Because the large size of this minimal co-segregating region would make positional cloning strategies intactable, additional genetic pointers were sought which focused the search for the AD3 gene to one or more subregions within the interval flanked by D14S53 and D14S258. Haplotype analyses at the markers between D14S53 and D14S258 failed to detect statistically significant evidence for linkage disequilibrium and/or allelic association between the FAD trait and alleles at any of these markers, irrespective of whether the analyses were restricted to those pedigrees with early onset forms of FAD, or were generalized to include all pedigrees. This result was not unexpected given the diverse ethnic origins of our pedigrees. However, when pedigrees of similar ethnic descent were collated, direct inspection of the haplotypes observed on the disease bearing chromosomes segregating in different pedigrees of similar ethnic origin revealed two clusters of marker loci (Table 2). The first of these clusters located centromeric to D14S77 (D14S786, D14S277 and D14S268) and spanned the 0.95 Mb physical interval contained in YAC 78842 (depicted as region B in FIG. **1***c*). The second cluster was located telomeric to D14S77 (D14S43, D14S273, and D14S76) and spanned the ~1 Mb physical interval included within the overlapping YAC clones 964c2, 74163, 797d11 and part of 854f5 (depicted as region A in FIG. **1***c*). Identical alleles were observed in at least two pedigrees from the same ethnic origin (Table 2). As part of the strategy, it was reasoned that the presence of shared alleles at one of these groups of physically clustered marker loci might reflect the co-inheritance of a small physical region surrounding the ARMP gene on the original founder chromosome in each ethnic population. Significantly, each of the shared extended haplotypes were rare in normal Caucasian populations and allele sharing was not observed at other groups of markers spanning similar genetic intervals elsewhere on chromosome 14q24.3.

Transcription Mapping and Preliminary Analysis of Candidate Genes

To isolate expressed sequences encoded within both critical intervals, a direct selection strategy was used in involving immobilized, cloned, human genomic DNA as the hybridization target to recover transcribed sequences from primary complementary DNA pools derived from human brain mRNA (Rommens et al., 1993). Approximately 900 putative cDNA fragments of size 100 to 600 base pairs were recovered from regions A and B in FIG. **1***c*. These fragments were hybridized to Southern blots containing genomic DNAs from each of the overlapping YAC clones and genomic DNAs from humans and other mammals. This identified a subset of 151 clones which showed evidence for evolutionary conservation and/or for a complex structure which suggested that they were derived from spliced mRNA. The clones within this subset were collated on the basis of physical map location, cross-hybridization and nucleotide sequence, and were used to screen conventional human brain cDNA libraries for longer cDNAs. At least 19 independent cDNA clones over 1 kb in length were isolated and then aligned into a partial transcrip-

tion map of the AD3 region (FIG. 1*d*). Only three of these transcripts corresponded to known characterized genes (cFOS, dihydrolipoamide succinyl transferase and latent transforming growth factor binding protein 2).

Recovery of Potential Candidate Genes

Each of the open reading frame portions of the candidate genes were recovered by RT-PCR from mRNA isolated from post-mortem brain tissue of normal control subjects and from either post-mortem brain tissue or cultured fibroblast cell lines of affected members of six pedigrees definitively linked to chromosome 14. The RT-PCR products were then screened for mutations using chemical cleavage and restriction endonuclease fingerprinting single-strand sequence conformational polymorphism methods (Saleeba and Cotton, 1993; Liu and Sommer, 1995), and by direct nucleotide sequencing. With one exception, all of the genes examined, although of interest, were not unique to affected subjects, and did not co-segregate with the disease. The single exception was the candidate gene represented by clone S182 which contained a series of nucleotide changes not observed in normal subjects, but which altered the predicted amino acid sequence in affected subjects. Although nucleotide sequence differences were also observed in some of the other genes, most were in the 3' untranslated regions and none were unique to Ad-affected subjects.

The remaining sequences, a subset of which are mapped in FIG. 1*b* together with additional putative transcriptional sequences not identified in FIG. 1*c*, are identified in the sequence listings as 14 through 43. The SEQ ID NOS:14 to 43 represent neighbouring genes or fragments of neighbouring genes adjacent the hARMP gene or possibly additional coding fragments arising from alternative splicing of the hARMP. SEQ ID NOS:44-126 and SEQ ID NOS:150-160 represent neighboring genomic fragments containing both exon and intron information. Such sequences are useful for creating primers, for creating diagnostic tests, creating altered regulatory sequences and use of adjacent genomic sequences to create better animal models.

Characterization of the hARMP Gene

Hybridization of the S182 clone to northern blots identified a transcript expressed widely in many areas of brain and peripheral tissues as a major 3.0 kb transcript and a minor transcript of 7.0 kb. Although the identity of the ~7.0 kb transcript is unclear, two observations suggest that the ~3.0 kb transcript represents an active product of the gene. Hybridization of the S182 clone to northern blots containing mRNA from a variety of murine tissues, including brain, identifies only a single transcript identical in size to the ~3.0 kb human transcript. All of the longer cDNA clones recovered to date (2.6-2.8 kb), which include both 5' and 3' UTRs and which account for the ~3.0 kb band on the northern blot, have mapped exclusively to the same physical region of chromosome 14. From these experiments the ~7.0 kb transcript could represent either a rare alternatively spliced or polyadenylated isoform of the ~3.0 transcript or could represent another gene with homology to S182.

The nucleotide sequence of the major transcript was determined from the consensus of eleven independent longer cDNA clones and from 3 independent clones recovered by standard 5' rapid amplification of cDNA ends and bears no significant homology to other human genes. The cDNA of the sequenced transcript is provided in SEQ ID NO:1 and the predicted amino acid sequence is provided in SEQ ID NO:2. The cDNA sequence of another sequenced human clone is also provided as SEQ ID NO:133 and its predicted amino acid sequence is provided in SEQ ID NO:134.

Analysis of the 5' end of multiple cDNA clones and RT-PCR products as well as corresponding genomic clones indicates that the 5' UTR is contained within at least two exons and that transcription either begins from two different start sites and/or that one of the early 5' untranslated exons is alternatively spliced (Table 6). The longest predicted open reading frame contains 467 amino acids with a small alternatively spliced exon of 4 aminc acids at 25 codons from the putative start codon (Table 3). This putative start codon is the first in phase ATG located 63 bp downstream of a TGA stop codon and lacks a classical Kozak consensus sequences around the first two in-phase ATG sequences (Rogaer et al., in preparation). Like other genes lacking classical 'strong' start codons, the putative 5' UTR of the human transcripts are rich in GC.

Comparison of the nucleic acid and predicted amino acid sequences with available databases using the BLAST alignment paradigms revealed modest amino acid similarity with the *C. elegans* sperm integral membrane protein SPE-4 ($p=1.5\ e^{25}$, 24-37% identity over three groups of at least fifty residues) and weaker similarity to portions of several other membrane spanning proteins including mammalian chromogranin A and alpha subunit of mammalian voltage dependent calcium channels (Altschul et al., 1990). This clearly established that they are not the same gene. The amino-acid sequence similarities across putative transmembrane domains may occasionally yield alignment that simply arises from the limited number of hydrophobic amino acids, but there is also extended sequence alignment between S182 protein and SPE-4 at several hydrophillic domains. Both the putative S182 protein and SPE-4 are predicted to be of comparable size (467 and 465 residues, respectively) and to contain at least seven transmembrane domains with a large acidic domain preceding the final predicted transmembrane domains with a large acidic domain preceding the final predicted transmembrane domain. The S182 protein does have a longer predicted hydrophillic region at the N terminus.

Further investigation of the hARMP has revealed a host of sequence fragments which form the hARMP gene and include intron sequence information, 5' end untranslated sequence information and 3' end untranslated sequence information (Table 6). Such sequence fragments are identified in Sequence ID Nos. 6 to 13.

Mutations in the S182 Transcript

Direct sequencing of overlapping RT-PCR products spanning the 3.0 kb S182 transcript isolated from affected members of the six large pedigrees linked to chromosome 14 led to the discovery of eight missense mutations in each of the six pedigrees (Table 7, FIG. **2**). Each of these mutations co-segregated with the disease in the respective pedigrees [FIG. **3**(*a*) (*b*) (*c*) (*d*) (*e*)], and were absent from 142 unrelated neurologically normal subjects drawn from the same ethnic origins as the FAD pedigrees (284 unrelated chromosomes).

The location of the gene within the physical interval segregating with AD3 trait, the presence of eight different missense mutations which co-segregate with the disease train in six pedigrees definitively linked to chromosome 14, and the absence of these mutations in 284 independent normal chromosomes cumulatively confirms that the hARMP gene is the AD3 locus. Further biologic support for this hypothesis arises from the fact that the residues mutated in FAD kindreds are conserved in evolution (Table 3) and occur in domains of the protein which are also highly conserved, and from the fact that the S182 gene product is expressed at high levels in most regions of the brain including the most severely affected with AD.

The DNA sequence for the hARMP gene as cloned has been incorporated into a plasmid Bluescript. This stable vector has been deposited at ATCC under accession number 97124 on Apr. 28, 1995.

Several mutations in the hARMP gene have been identified which cause a severe type of familial Alzheimer's Disease. One, or a combination of these mutations may be responsible for this form of Alzheimer's Disease as well as several other neurological disorders. The mutations may be any form of nucleotide sequence alteration or substitution. Specific disease causing mutations in the form of nucleotide and/or amino acid substitutions have been located, although we anticipate additional mutations will be found in other families. Each of these nucleotide substitutions occurred within the putative ORF of the S182 transcript, and would be predicted to change the encoded amino acid at the following positions, numbering from the first putative initiation codon. The mutations are listed in respect of their nucleotide locations in SEQ ID NO:1 and SEQ ID NO:133 (an additional human clone) and amino acid locations in SEQ ID NO:2 and SEQ ID NO:134 (the additional human clone).

i)	685, A→C	Met 146 Leu
ii)	737, A→G	His 163 Arg
iii)	986, C→A	Ala 246 Glu
iv)	1105, C→G	Leu 286 Val
v)	1478, G→A	Cys 410 Tyr
vi)	1027, C→T	Ala 260 Val
vii)	1102, C→T	Ala 285 Val
viii)	1422, C→G	Leu 392 Val

The Met146Leu, Ala246Glu and Cys410Tyr mutations have not been detected in the genomic DNA of affected members of the eight remaining small early onset autosomal dominant FAD pedigrees or six additional families in our collection which express late FAD onset. We predict that such mutations would not commonly occur in late onset FAD which has been excluded by genetic linkage studies from the more aggressive form of AD linked to chromosome 14q24.3 (St. George-Hyslop, P et al., 1992; Schellenberg et al., 1993). The His163Arg mutation has been found in the genomic DNA of affected members of one additional FAD pedigree for which positive but significant statistical evidence for linkage to 14 becomes established. Age of onset of affected members was consistent with affected individuals from families linked to chromosome 14.

Mutations Ala260Val, Ala285Val, and Leu392Val all occur within the acidic hydrophilic loop between putative transmembrane 6 (TM6) and transmembrane (TM7) (FIG. **6**). Two of the mutations (A260V; A285V) and the L286V mutation are also located in the alternative spliced domain.

All eight of the mutations can be assayed by a variety of strategies (direct nucleotide sequencing, allele specific oligos, ligation polymerase chain reaction, SSCP, RFLPs etc.) using RT-PCR products representing the mature mRNA/cDNA sequence or genomic DNA. Allele specific oligos were chosen for assaying the mutations. For the A260V and the A285V mutations, genomic DNA carrying the exon was amplified using the same PCR primers and methods as for the L286V mutation. PCR products were then denatured and slot blotted to duplicate nylon membranes using the slot blot protocol described for the C410T mutation.

Of all of the nucleotide substitutions co-segregated with the disease in their respective pedigrees, none were seen in asymptomatic family members aged more than two standard deviations beyond the mean age of onset, and none were present on 284 chromosomes from unrelated neurologically normal subjects drawn from comparable ethnic origins.

Identification of an Alternative Splice Form of the ARMP Gene Product

During sequencing studies of RT-PCR products for the ARMP gene recovered from a variety of tissues, it was discovered that some peripheral tissues (principally white blood cells) demonstrated two alternative splice forms of the ARMP gene. One form is identical to the (putatively 467 amino acid) isoform constitutatively expressed in all brain regions. The alternative splice form results from the exclusion of the segment of the cDNA between base pairs 1018 and 1116 inclusive, and results in a truncated isoform of the ARMP protein wherein the hydrophobic part of the hydrophilic acidically-charged loop immediately C-terminal to TM6 is removed. This alternatively spliced isoform therefore is characterized by preservation of the sequence N-terminal to and including the tyrosine at position 256, changing of the aspartate at 257 to alanine, and splicing on to the C-terminal part of the protein from and including tyrosine 291. Such splicing differences are often associated with important functional domains of the proteins. This argues that this hydrophilic loop (and consequently the N-terminal hydrophilic loop with similar amino acid charge) is/are active functional domains of the ARMP product and thus sites for therapeutic targeting.

ARMP Protein

With respect to DNA SEQ ID NO.1 and DNA SEQ ID NO:133, analysis of the sequence of overlapping cDNA clones predicted an ORF protein of 467 amino acids when read from the first in phase ATG start codon and a molecular mass of approximately 52.6 kDa as later described, due to either polymorphisms in the protein or alternate splicing of the transcript, the molecular weight of the protein can vary due to possible substitutions or deletions of amino acids.

The analysis of predicted amino acid sequence using the Hopp and Woods algorithm suggested that the protein product is a multispanning integral membrane protein such as a receptor, a channel protein, or a structural membrane protein. The absence of recognizable signal peptide and the paucity of glycoslyation sites are noteworthy, and the hydropathy profile suggests that the protein is less likely to be a soluble protein with a highly compact three-dimensional structure.

The protein may be a cellular protein with a highly compact three dimensional structure in which respect is may be similar to APOE which is also related to Alzheimer's Disease. In light of this putative functional role, it is proposed that this protein be labeled as the Alzheimer Related Membrane Protein (ARMP). The protein also contains a number of potential phosphorylation sites, one of which is the consensus site for MAP kinase which is also involved in the hyperphosphorlyation of tau during the normal conversion of normal tau to neurofibrillary tangles. This consensus sequence may provide a common putative pathway linking this protein and other known biochemical aspects of Alzheimer's Disease and would represent a likely therapeutic target. Review of the protein structure reveals two sequence YTPF (residues 115-119) SEQ ID NO:161 and STPE (residues 353-356) SEQ ID NO:162 which represent the 5/T-P motif which is the MAP kinase consensus sequence. Several other phosphorylation sites exist with consensus sequences for Protein Kinase C activity. Because protein kinase C activity is associated with differences in the metabolism of APP which are relevant to

Alzheimer's Disease, these sites on the ARMP protein and homologues are sites for therapeutic targeting.

The N-terminal is characterized by a highly hydrophilic acid charged domain with several potential phosphorylation domains, followed sequentially by a hydrophobic membrane spanning domain of 19 residues; a charged hydrophilic loop, then five additional hydrophobic membrane spanning domains interspersed with short (5-20 residue) hydrophilic domains; an additional larger acidic hydrophilic charged loop, and then at least one and possibly two other hydrophobic potentially membrane spanning domains culminating in a polar domain at the C-terminus (Table 4 and FIG. **6**B). The presence of seven membrane spanning domains is characteristic of several classes of G-coupled receptor proteins but is also observed with other proteins including channel proteins.

Comparison of the nucleic acid and predicted amino acid sequences with available databases using the BLAST alignment paradigms revealed amino acid similarity with the *C. elegans* sperm integral membrane protein spe-4 and a similarity to several other membrane spanning proteins including mammalian chromogranin A and the α-subunit of mammalian voltage dependent calcium channels.

The similarity between the putative products of the spe-4 and ARMP genes implies that they may have similar activities. The SPE-4 protein of *C. elegans* appears to be involved in the formation and stabilization of the fibrous body-membrane organelle (FMBO) complex during spermatogenesis. The FBMO is a specialized Golgi-derived organelle, consisting of a membrane bound vesicle attached to and partly surrounding a complex of parallel protein fibers and may be involved in the transport and storage of soluble and membrane-bound polypeptides. Mutations in spe-4 disrupt the FBMO complexes and arrest spermatogenesis. Therefore the physiologic function of spe-4 may be either to stabilize interactions between integral membrane budding and fusion events, or to stabilize interactions between the membrane and fibrillary proteins during the intracellular transport of the FBMO complex during spermatogenesis. Comparable functions could be envisaged for the ARMP. The ARMP could be involved either in the docking of other membrane-bound proteins such as βAPP, or the axonal transport and fusion budding of membrane-bound vesicles during protein transport such as in the golgi apparatus or endosome-lysosome system. If correct, then mutations might be expected to result in aberrant transport and processing of βAPP and/or abnormal interactions with cytoskeletal proteins such as the microtubule-associated protein Tau. Abnormalities in the intracellular and in the extracellular disposition of both βAPP and Tau are in fact an integral part of the neuropathologic features of Alzheimer's Disease. Although the location of the ARMP mutations in highly conserved residues within conserved domains of the putative proteins suggests that they are pathogenic, at least three of these mutations are conservative which is commensurate with the onset of disease in adult life. Because none of the mutations observed so far are deletions or nonsense mutations that would be expected to cause a loss of function, we cannot predict whether these mutations will have a dominant gain-of-function effect and promote aberrant processing of βAPP or a dominant loss-of-function effect causing arrest of normal βAPP processing.

An alternative possibility is that the ARMP gene product may represent a receptor or channel protein. Mutations of such proteins have been causally related to several other dominant neurologic disorders in both vertebrate (e.g., Malignant hyperthermia, hyperkalemic periodic paralysis in humans) and in invertebrate organisms (deg-1(d) mutants in *C. elegans*). Although the pathology of these other disorders does not resemble that of Alzheimer's Disease there is evidence for functional abnormalities in ion channels in Alzheimer's Disease. For example, anomalies have been reported in the tetra-ethylammonium-sensitive 113 pS potassium channel and in calcium homeostasis. Perturbations in transmembrane calcium fluxes might be especially relevant in view of the weak homology between S182 and the α-ID subunit of voltage-dependent calcium channels and the observations that increases in intracellular calcium in cultured cells can replicate some of the biochemical features of Alzheimer's Disease such as alteration in the phosphorylation of Tau-microtubule-associated protein and increased production of Aβ peptides.

As mentioned purified normal ARMP protein is characterized by a molecular weight of 52.6 kDa. The normal ARMP protein, substantially free of other proteins, is encoded by the aforementioned SEQ ID NO:1 and SEQ ID NO:133. As will be later discussed, the ARMP protein and fragments thereof may be made by a variety of methods. Purified mutant ARMP protein is characterized by FAD-associated phenotype (necrotic death, apoptic death, granulovascular degeneration, neurofibrillary degeneration, abnormalities or changes in the metabolism of APP, and Ca^{2+}, K^+ and glucose, and mitochondrial function and energy metabolism neurotransmitter metabolism, all of which have been found to be abnormal in human brain, and/or peripheral tissue cells in subjects with Alzheimer's Disease) in a variety of cells. The mutant ARMP, free of other proteins, is encoded by the mutant DNA sequence.

Description of the E5-1 Gene, a Homologue of the ARMP Gene

A gene, E5-1, with substantial nucleotide and amino acid homology to the ARMP gene was identified by using the nucleotide sequence of the cDNA for ARMP to search data bases using the BLASTN paradigm of Atschul et al., 1990. Three expressed sequence tagged sites (ESTs) identified by accession numbers T03796, R14600, and R05907 were located which had substantial homology ($p<1.0\,e^{-100}$, greater than 97% identity over at least 100 contiguous base pairs).

Oligonucleotide primers were produced from these sequences and used to generate PCR products by reverse transcriptase PCR (RT-PCR). These short RT-PCR products were partially sequenced to confirm their identity with the sequences within the data base and were then used as hybridization probes to screen full-length cDNA libraries. Several different cDNA's ranging in size from 1 Kb to 2.3 Kb were recovered from a cancer cell cDNA library (CaCo-2) and from a human brain cDNA library (E5-1, G1-1, cc54, cc32).

The nucleotide sequence of these clones confirmed that all were derivatives of the same transcript (designated E5-1). A plasmid including this nucleic acid was deposited with the ATCC under the terms of the Budapest Treaty on Jun. 28, 1995 and has been assigned ATCC accession number 97214.

The gene encoding the E5-1 transcript mapped to human chromosome 1 using hybrid mapping panels and to two clusters of CEPH Mega YAC clones which have been placed upon a physical contig map (YAC clones 750g7, 921d12 mapped by FISH to 1q41; and YAC clone 787g12 which also contains an EST of the leukemia associated phosphoproteins (LAP18) gene which has been mapped to 1p36.1-p35) (data not shown).

Hybridization of the E5-1 cDNA clones to Northern Blots detected an ~2.3 kilobase mRNA band in many tissues including regions of the brain, as well as a ~2,6 K.b mRNA band in muscle, cardiac muscle and pancreas (FIG. **7**).

In skeletal muscle, cardiac muscle and pancreas, the E5-1 gene is expressed at relatively higher levels than in brain and as two different transcripts of ~2.3 Kb and ~2.6 Kb. Both of the E5-1 transcripts have sizes clearly distinguishable from that of the 2.7 Kb ARMP transcript, and did not cross-hybridize with ARMP probes at high stringency. The cDNA sequence of the E5-1 gene is identified as SEQ ID NO.:137.

The longest ORF within the E5-1 cDNA consensus nucleotide sequence predicts a polypeptide containing 448 amino acids (numbering from the first in-phase ATG codon which was surrounded by a GCC-agg-GCt-ATG-c Kozak consensus sequence) (SEQ ID NO.:138).

A comparison of the amino acid sequences of hARMP and E5-1 homologue protein are shown in Table 8. Identical residues are indicated by vertical lines. The locations of mutations in the E5-1 gene are indicated by downward pointing arrows. The locations of the mutations in the hARMP gene are indicated by upward pointing arrows. Putative TM domains are in open ended boxes. The alternatively spliced exons are denoted by superscripted (E5-1) or subscripted (hARMP) "*".

BLASTP alignment analyses also detected significant homology with SPE-4 of *C. elegans* (P=3.5 e−26; identity=20-63% over five domains of at least 22 residues), and weak homologies to brain sodium channels (alpha III subunit) and to the alpha subunit of voltage dependent calcium channels from a variety of species (P=0.02; identities 20-28% over two or more domains each of at least 35 residues) (Atschul, 1990). These alignments are similar to those described above for the ARMP gene. However, the most striking homology to the E5-1 protein was found with the amino acid sequence predicted for ARMP. ARMP and E-51 proteins share 63% overall amino acid sequence identity, and several domains display virtually complete identity (Table 8). Furthermore, all eight residues mutated in ARMP in subjects with AD3 are conserved in the E5-1 protein (Table 8). As would be expected, hydrophobicity analyses suggest that both proteins also share a similar structural organization.

The similarity was greatest in several domains of the protein corresponding to the intervals between transmembrane domain 1 (TM1) and TM6, and from TM7 to the C-terminus of the ARMP gene. The main difference from ARMP is a difference in the size and amino acid sequence of the acidically-charged hydrophilic loop in the position equivalent to the hydrophilic loop between transmembrane domains TM6 and TM7 in the ARMP protein and in the sequence of the N-terminal hydrophilic domains.

Thus, both proteins are predicted to possess seven hydrophobic putative transmembrane domains, and both proteins bear large acidic hydrophilic domains at the N-terminus and between TM6 and TM7 (FIGS. **6** and **8**). A further similarity arose from analysis of RT-PCR products from brain and muscle RNA, which revealed that nucleotides 1153-1250 of the E5-1 transcript are alternatively spliced. These nucleotides encode amino acids 263-296, which are located within the TM6-TM7 loop domain of the putative E5-1 protein, and which share 94% sequence identity with the alternatively spliced residues 257-290 in ARMP.

The most noticeable differences between the two predicted amino acid sequences occur in the amino acid sequence in the central portion of the TM6-TM7 hydrophilic loop (residues 304-374 of ARMP; 301-355 of E5-1), and in the N-terminal hydrophilic domain (Table 8). By analogy, this domain is also less highly conserved between the murine and human ARMP genes (identity=47/60 residues), and shows no similarity with the equivalent region of SPE-4.

A splice variant of the E5-1 cDNA sequence identified as SEQ ID NO:137 has also been found in all tissues examined. This splice variant lacks the tripet GAA at nucleotide positions 1338-1340.

A further variant has been found in one normal individual whose E5-1 cDNA had C replacing T at nucleotide position 626, which does not change the amino acid sequence.

Mutations of the E5-1 Gene Associated with Alzheimer's Disease

The strong similarity between ARMP and the E5-1 gene product raised the possibility that the E5-1 gene might be the site of disease-causing mutations in some of a small number of early onset AD pedigrees in which genetic linkage studies have excluded chromosomes 14, 19 and 21. RT-PCR was used to isolate cDNAs corresponding to the E5-1 transcript from lymphoblasts, fibroblasts or post-mortem brain tissue of affected members of eight pedigrees with early onset familial AD (FAD) in which mutations in the β APP and ARMP gene had previously been excluded by direct sequencing studies.

Examination of these RT-PCR products detected a heterozygous. A→G substitution at nucleotide 1080 in all four affected members of an extended pedigree of Italian origin (Flo10) with early onset, pathologically confirmed FAD (onset=50-70 yrs.). This mutation would be predicted to cause a Met→Val missense mutation at codon 239 (Table 8).

A second mutation (A→T at nucleotide 787) causing a Asn→Ile substitution at codon 141 was found in affected members of a group of related pedigrees of Volga German ancestry (represented by cell lines AG09369, AG09907, AG09952, and AG09905, Coriell Institute, Camden, N.J.) Significantly, one subject (AG09907) was homozygous for this mutation, an observation compatible with the inbred nature of these pedigrees. Significantly, this subject did not have a significantly different clinical picture from those subjects heterozygous for the Arg14Ile mutation. Neither of the E5-1 gene mutations were found in 284 normal Caucasian controls nor were they present in affected members of pedigrees with the AD3 type of AD.

Both of these mutations would be predicted to cause substitutions of residues which are highly conserved within the ARMP/E5-1 gene family.

The finding of a gene whose product is predicted to share substantial amino acid and structural similarities with the ARMP gene product suggest that these proteins may be functionally related either as independent proteins with overlapping functions but perhaps with slightly different specific activities, as physically associated subunits of a multimeric polypeptide or as independent proteins performing consecutive functions in the same pathway.

The observation of two different missense mutations in conserved domains of the E5-1 protein in subjects with a familial form of AD argues that these mutations are, like those in the ARMP gene, causal to AD. This conclusion is significant because, while the disease phenotypes associated with mutations in the ARMP gene (onset 30-50 yrs., duration 10 years) are subtly different from that associated with mutations in the E5-1 gene (onset 40-70 years; duration up to 20 years), the general similarities clearly argue that the biochemical pathway subsumed by members of this gene family is central to the genesis of at least early onset AD. The subtle differences in disease phenotype may reflect a lower level of expression of the E5-1 transcript in the CNS, or may reflect a different role for the E5-1 gene product.

By analogy to the effects of ARMP mutations, E5-1 when mutated may cause aberrant processing of APP (Amyloid Precursor Protein) into Aβ peptide, hyperphosphorylation of

Tau microtubule associated protein and abnormalities of intracellular calcium homeostasis. Interference with these anomalous interactions provides a potential therapy for AD.

Functional Domains of the ARMP Protein are Defined by Splicing Sites and Similarities within Other Members of a Gene Family

The ARMP protein is a member of a novel class of transmembrane proteins which share substantial amino acid homology. The homology is sufficient that certain nucleotides probes and antibodies raised against one can identify other members of this gene family. The major difference between members of this family reside in the amino acid and nucleotide sequence homologous to the hydrophillic acid loop domain between putative transmembrane 6 and transmembrane 7 domains of the ARMP gene and gene product. This region is alternatively spliced in some non-neural tissues, and is also the site of several pathogenic disease-causing mutations in the ARMP gene. The variable splicing of this hydrophilic loop, the presence of a high-density of pathogenic mutations within this loop, and the fact that the amino acid sequences of the loop differs between members of the gene family suggest that this loop is an important functional domain of the protein and may confer some specificity to the physiologic and pathogenic interactions which the ARMP gene product undergoes because the N-terminal hydrophilic domain shares the same acidic charge and same orientation with respect to the membrane, it is very likely that these two domains share functionality either in a coordinated (together) or independent fashion (e.g., different ligands or functional properties). As a result everything said about the hydrophilic loop shall apply also to the N-terminal hydrophilic domain.

Knowledge of the specificity of the loop can be used to identify ligands and functional properties of the ARMP gene product (e.g. sites of interactions with APP, cytosolic proteins such as kinases, Tau, and MAP, etc.). Soluble recombinant fusion proteins can be made or the nucleotide sequence coding for amino acids within the loop or parts of the loop can be expressed in suitable vectors (yeast-2-hybrid, baculovirus, and phage-display systems for instance), and used to identify other proteins which interact with ARMP in the pathogenesis of Alzheimer's Disease and other neurological and psychiatric diseases. Therapies can be designated to modulate these interactions and thus to modulate Alzheimer's Disease and the other conditions associated with acquired or inherited abnormalities of the ARMP gene or its gene products. The potential efficacy of these therapies can be tested by analyzing the affinity and function of these interactions after exposure to the therapeutic agent by standard pharmacokinetic measurements of affinity (Kd and Vmax etc.) using synthetic peptides or recombinant proteins corresponding to functional domains of the ARMP gene (or its homologues). An alternate method for assaying the effect of any interactions involving functional domains such as the hydrophilic loop is to monitor changes in the intracellular trafficking and post-translational modification of the ARMP gene by in-situ hybridization, immunohistochemistry, Western blotting and metabolic pulse-chase labeling studies in the presence of and in the absence of the therapeutic agents. A third way is to monitor the effects of "downstream" events including (i) changes in the intracellular metabolism, trafficking and targeting of APP and its products; (ii) changes in second messenger event e.g., cAMP, intracellular Ca^{++} protein kinase activities, etc.

Isolation and Purification of the ARMP Protein

The ARMP protein may be isolated and purified by methods selected on the basis of properties revealed by its sequence. Since the protein possesses properties of a membrane-spanning protein, a membrane fraction of cells in which the protein is highly expressed (e.g., central nervous system cells or cells from other tissues) would be isolated and the proteins removed by extraction and the proteins solubilized using a detergent.

Purification can be achieved using protein purification procedures such as chromatography methods (gel-filtration, ion-exchange and immunoaffinity), by high-performance liquid chromatography (RP-HPLC, ion-exchange HPLC, size-exclusion HPLC, high-performance chromatofocusing and hydrophobic interaction chromatography) or by precipitation (immunoprecipitation). Polyacrylamide gel electrophoresis can also be used to isolate the ARMP protein based on its molecular weight, charge properties and hydrophobicity.

Similar procedures to those just mentioned could be used to purify the protein from cells transfected with vectors containing the ARMP gene (e.g., baculovirus system, yeast expression systems, eukaryotic expression systems).

Purified protein can be used in further biochemical analyses to establish secondary and tertiary structure which may aid in the design of pharmaceuticals to interact with the protein, alter protein charge configuration or charge interaction with other proteins, lipid or saccharide moieties, alter its function in membranes as a transporter channel or receptor and/or in cells as an enzyme or structural protein and treat the disease.

The protein can also be purified by creating a fusion protein by legating the ARMP cDNA sequence to a vector which contains sequence for another peptide (e.g., GST-glutathionine succinyl transferase). The fusion protein is expressed and recovered from prokaryotic (e.g., bacterial or baculovirus) or eukaryotic cells. The fusion protein can then be purified by affinity chromatography based upon the fusion vector sequence. The ARMP protein can then be further purified from the fusion protein by enzymatic cleavage of the fusion protein.

Isolating Mouse ARMP Gene

In order to characterize the physiological significance of the normal and mutant hARMP gene and gene products in a transgenic mouse model it was necessary to recover a mouse homologue of the hARMP gene. We recovered a murine homologue for the hARMP gene by screening a mouse cDNA library with a labelled human DNA probe and in this manner recovered a 2 kb partial transcript (representing the 3' end of the gene) and several RT-PCR products representing the 5' end. Sequencing of the consensus cDNA transcript of the murine homologue revealed substantial amino acid identity. The sequence cDNA is identified in SEQ ID NO:3 and the predicted amino acid sequence is provided in SEQ ID NO:4. Further sequencing of the mouse cDNA transcript has provided the sequence of the complete coding sequence identified as SEQ ID NO:135 and the predicted amino acid sequence from this sequence is provided in SEQ ID NO:136. More importantly, all of the amino acids that were mutated in the FAD pedigrees were conserved between the murine homologue and the normal human variant (Table 3). This conservation of the ARMP gene as is shown in Table 3, indicates that an orthologous gene exists in the mouse (mARMP), and it is now possible to clone mouse genomic libraries using human ARMP probes. This will also make it possible to identify and characterize the ARMP gene in other species. This also provides evidence of animals with various disease states or disorders currently known or yet to be elucidated.

Transgenic Mouse Model

The creation of a mouse model for Alzheimer's Disease is important to the understanding of the disease and for the testing of possible therapies. Currently no unambiguous viable animal model for Alzheimer's Disease exists.

There are several ways in which to create an animal model for Alzheimer's Disease. Generation of a specific mutation in the mouse gene such as the identified hARMP gene mutations is one strategy. Secondly, we could insert a wild type human gene and/or humanize the murine gene by homologous recombination. Thirdly, it is also possible to insert a mutant (single or multiple) human gene as genomic or minigene cDNA constructs using wild type or mutant or artificial promoter elements. Fourthly, knock-out of the endogenous murine genes may be accomplished by the insertion of artificially modified fragments of the endogenous gene by homologous recombination. The modifications include insertion of mutant stop codons, the deletion of DNA sequences, or the inclusion of recombination elements (lcx p sites) recognized by enzymes such as Cre recombinase.

To inactivate the mARMP gene chemical or x-ray mutagenesis of mouse gametes, followed by fertilization, can be applied. Heterozygous offspring can then be identified by Southern blotting to demonstrate loss of one allele by dosage, or failure to inherit one parental allele using RFLP markers.

To create a transgenic mouse a mutant version of hRMP or mARMP can be inserted into a mouse germ line using standard techniques of oocyte microinjection or transfection or microinjection into stem cells. Alternatively, if it is desired to inactivate or replace the endogenous mARMP gene, homologous recombination using embryonic stem cells may be applied.

For oocyte injection, one or more copies of the mutant or wild type ARMP gene can be inserted into the pronucleus of a just-fertilized mouse oocyte. This oocyte is then reimplanted into a pseudo-pregnant foster mother. The liveborn mice can then be screened for integrants using analysis of tail DNA for the presence of human ARMP gene sequences. The transgene can be either a complete genomic sequence injected as a YAC, BAC, PAC or other chromosome DNA fragment, a cDNA with either the natural promoter or a heterologous promoter, or a minigene containing all of the coding region and other elements found to be necessary for optimum expression.

Retroviral infection of early embryos can also be done to insert the mutant or wild type hARMP. In this method, the mutant or wild type hARMP is inserted into a retroviral vector which is used to directly infect mouse embryos during the early stages of development to generate a chimera, some of which will lead to germline transmission. Similar experiments can be conducted in the cause of mutant proteins, using mutant murine or other animal ARMP gene sequences.

Homologous recombination using stem cells allows for screening of gene transfer cells to identify the rare homologous recombination events. Once identified, these can be used to generate chimeras by injection of mouse blastocysts, and a proportion of the resulting mice will show germline transmission from the recombinant line. This methodology is especially useful if inactivation of the mARMP gene is desired. For example, inactivation of the mARMP gene can be done by designing a DNA fragment which contains sequences from a mARMP exon flanking a selectable marker. Homologous recombination leads to the insertion of the marker sequences in the middle of an exon, inactivating the mARMP gene. DNA analysis of individual clones can then be used to recognize the homologous recombination events.

It is also possible to create mutations in the mouse germline by injecting oligonucleotides containing the mutation of interest and screening the resulting cells by PCR.

This embodiment of the invention has the most significant commercial value as a mouse model for Alzheimer's Disease. Because of the high percentage of sequence conservation between human and mouse it is contemplated that an orthologous gene will exist also in many other species. It is thus contemplated that it will be possible to generate other animal models using similar technology.

Screening and Diagnosis for Alzheimer's Disease General Diagnostic Uses of the ARMP Gene and Gene Product

The ARMP gene and gene products will be useful for diagnosis of Alzheimer's Disease, presenile and senile dementias, psychiatric diseases such as schizophrenia, depression, etc., and neurologic diseases such as stroke and cerebral hemorrhage—all of which are seen to a greater or lesser extent in symptomatic subjects bearing mutations in the ARMP gene or in the APP gene. Diagnosis of inherited cases of these diseases can be accomplished by analysis of the nucleotide sequence (including genomic and cDNA sequences included in this patent). Diagnosis can also be achieved by monitoring alterations in the electrophoretic mobility and by the reaction with specific antibodies to mutant or wild-type ARMP gene products, and by functional assays demonstrating altered function of the ARMP gene product. In addition, the ARMP gene and ARMP gene products can be used to search for inherited anomalies in the gene and/or its products (as well as those of the homologous gene) and can also be used for diagnosis in the same way as they can be used for diagnosis of non-genetic cases.

Diagnosis of non-inherited cases can be made by observation of alterations in the ARMP transcription, translation, and post-translational modification and processing as well as alterations in the intracellular and extracellular trafficking of ARMP gene products in the brain and peripheral cells. Such changes will include alterations in the amount of ARMP messenger RNA and/or protein, alteration in phosphorylation state, abnormal intracellular location/distribution, abnormal extracellular distribution, etc. Such assays will include: Northern Blots (with ARMP-specific and ARMP non-specific nucleotide probes which also cross-react with other members of the gene family), and Western blots and enzyme-linked immunosorbent assays (ELISA) (with antibodies raised specifically to: ARMP; to various functional domains of ARMP; to other members of the homologous gene family; and to various post-translational modification states including glycosylated and phosphorylated isoforms). These assays can be performed on peripheral tissues (e.g., blood cells, plasma, cultured or other fibroblast tissues, etc.) as well as on biopsies of CNS tissues obtained antimortem or postmortem, and upon cerebrospinal fluid. Such assays might also include in-situ hybridization and immunohistochemistry (to localized messenger RNA and protein to specific subcellular compartments and/or within neuropathological structures associated with these diseases such as neurofibrillary tangles and amyloid plaques).

Screening for Alzheimer's Disease

Screening for Alzheimer's Disease as linked to chromosome 14 may now be readily carried out because of the knowledge of the mutations in the gene.

People with a high risk for Alzheimer's Disease (present in family pedigree) or, individuals not previously known to be at risk, or people in general may be screened routinely using probes to detect the present of a mutant ARMP gene by a variety of techniques. Genomic DNA used for the diagnosis

may be obtained from body cells, such as those present in the blood, tissue biopsy, surgical specimen, or autopsy material. The DNA may be isolated and used directly for detection of a specific sequence or may be PCR amplified prior to analysis. RNA or cDNA may also be used. To detect a specific DNA sequence hybridization using specific oligonucleotides, direct DNA sequencing, restriction enzyme digest, RNase protection, chemical cleavage, and ligase-mediated detection are all methods which can be utilized. Oligonucleotides specific to mutant sequences can be chemically synthesized and labelled radioactively with isotopes, or non-radioactively using biotin tags, and hybridized to individual DNA samples immobilized on membranes or other solid-supports by dot-blot or transfer from gels after electrophoresis. The presence or absence of these mutant sequences are then visualized using methods such as autoradiography, fluorometry, or calorimetric reaction. Examples of suitable PCR primers which are useful for example in amplifying portions of the subject sequence containing the aforementioned mutations are set out in Table 5. This table also sets out the change in enzyme site to provide a useful diagnostic tool as defined herein.

Direct DNA sequencing reveals sequence differences between normal and mutant ARMP DNA. Cloned DNA segments may be used as probes to detect specific DNA segments. PCR can be used to enhance the sensitivity of this method. PCR is an enzymatic amplification directed by sequence-specific primers, and involves repeated cycles of heat denaturation of the DNA, annealing of the complementary primers and extension of the annealed primer with a DNA polymerase. This results in an exponential increase of the target DNA.

Other nucleotide sequence amplification techniques may be used, such as ligation-mediated PCR, anchored PCR and enzymatic amplification as would be understood by those skilled in the art.

Sequence alterations may also generate fortuitous restriction enzyme recognition sites which are revealed by the use of appropriate enzyme digestion followed by gel-blot hybridization. DNA fragments carrying the site (normal or mutant) are detected by their increase or reduction in size, or by the increase or decrease of corresponding restriction fragment numbers. Genomic DNA samples may also be amplified by PCR prior to treatment with the appropriate restriction enzyme and the fragments of different sizes are visualized under UV light in the presence of ethidium bromide after gel electrophoresis.

Genetic testing based on DNA sequence differences may be achieved by detection of alteration in electrophoretic mobility of DNA fragments in gels. Small sequence deletions and insertions can be visualized by high resolution gel electrophoresis. Small deletions may also be detected as changes in the migration pattern of DNA heteroduplexes in non-denaturing gel electrophoresis. Alternatively, a single base substitution mutation may be detected based on differential PCR product length in PCR. The PCR products of the normal and mutant gene could be differentially detected in acrylamide gels.

Nuclease protection assays (S1 or ligase-mediated) also reveal sequence changes at specific location.

Alternatively, to confirm or detect a polymorphism restriction mapping changes ligated PCR, ASO, REF-SSCP chemical cleavage, endonuclease cleavage at mismatch sites and SSCP may be used. Both REF-SSCP and SSCP are mobility shift assays which are based upon the change in conformation due to mutations.

DNA fragments may also be visualized by methods in which the individual DNA samples are not immobilized on membranes. The probe and target sequences may be in solution or the probe sequence may be immobilized. Autoradiography, radioactive decay, spectrophotometry, and fluorometry may also be used to identify specific individual genotypes. Finally, mutations can be detected by direct nucleotide sequencing.

According to an embodiment of the invention, the portion of the cDNA or genomic DNA segment that is informative for a mutation, can be amplified using PCR. For example, the DNA segment immediately surrounding the C410Y mutation acquired from peripheral blood samples from an individual can be screened using the oligonucleotide primers 885 (tggagactggaacacaac) SEQ ID NO:127 and 893 (gtgtggccagggtagagaact) SEQ ID NO:128. This region would then be amplified by PCR, the products separated by electrophoresis, and transferred to membrane. Labelled oligonucleotide probes are then hybridized to the DNA fragments and autoradiography performed.

ARMP Expression

As an embodiment of the present invention, ARMP protein may be expressed using eukaryotic and prokaryotic expression systems. Eukaryotic expression systems can be used for many studies of the ARMP gene and gene product including determination of proper expression and post-translational modifications for full biological activity, identifying regulatory elements located in the 5' region of the ARMP gene and their role in tissue regulation of protein expression, production of large amounts of the normal and mutant protein for isolation and purification, to use cells expressing the ARMP protein as a functional assay system for antibodies generated against the protein or to test effectiveness of pharmacological agents, or as a component of a signal transduction system; to study the function of the normal complete protein, specific portions of the protein, or of naturally occurring and artificially produced mutant proteins.

Eukaryotic and prokaryotic expression systems were generated using two different classes of ARMP nucleotide cDNA sequence inserts. In the first class, termed full-length constructs, the entire ARMP cDNA sequence is inserted into the expression plasmid in the correct orientation, and includes both the natural 5' UTR and 3' UTR sequences as well as the entire open reading frame. The open reading frames bear a nucleotide sequence cassette which allows either the wild type open reading frame to be included in the expression system or alternatively, a single or a combination of double mutations can be inserted into the open reading frame. This was accomplished by removing a restriction fragment from the wild type open reading frame using the enzymes NarI and PflmI and replacing it with a similar fragment generated by reverse transcriptase PCR which bears the nucleotide sequence encoding either the Met146Leu mutation or the Hys163Arg mutation. A second restriction fragment was removed from the wild type normal nucleotide sequence for the open reading frame by cleavage with the enzymes PflmI and NcoI and replaced with restriction fragments bearing either nucleotide sequence encoding the Ala246Glu mutation, or the Ala260Val mutation or the Ala285Val mutation or the Leu286Val mutation, or the Leu392Val mutation, or the Cys410Tyr mutation. Finally, a third variant bearing combinations of either the Met146Leu or His163Arg mutations in tandem with the remaining mutations, was made by linking the NarI-PflmI fragment bearing these mutations and the PflmI-NcoI fragments bearing the remaining mutations.

A second variant of cDNA inserts bearing wild type or mutant cDNA sequences was constructed by removing from the full-length cDNA the 5' UTR and part of the 3' UTR

sequences. The 5' UTR sequence was replaced with a synthetic oligonucleotide containing a KpnI restriction site and a Kozak initiation site (oligonucleotide 969: ggtaccgccaccatgacagaggtacctgcac, SEQ ID NO:139). The 3' UTR was replaced with an oligonucleotide corresponding to position 2566 of the cDNA and bears an artificial EcoRI site (oligonucleotide 970: gaattcactggctgtagaaaaagac, SEQ ID NO:140). Mutant variants of this construct were then made by inserting the same mutant sequences described above at the NarI-PflmI fragment, and at the PsImI-NcoI sites described above.

For eukaryotic expressions, these various cDNA constructs bearing wild type and mutant sequences described above were cloned into the expression vector pZeoSV (invitrogen). For prokaryotic expression, two constructs have been made using the glutathione S-transferase fusion vector pGEX-kg. The inserts which have been attached to the GST fusion nucleotide sequence are the same nucleotide sequence described above (generated with the oligonucleotide primers 969, SEQ ID NO:139 and 970, SEQ ID NO:140) bearing either the normal open reading frame nucleotide sequence, or bearing a combination of single and double mutations as described above. This construct allows expression of the full-length protein in mutant and wild type variants in prokaryotic cell systems as a GST fusion protein which allows purification of the full length protein followed by removal of the GST fusion product by thrombin digestion. The second prokaryotic cDNA construct was generated to create a fusion protein with the same vector, and allows the production of the amino acid sequence corresponding to the hydrophilic acidic loop domain between TM6 and TM7 of the full-length protein, as either a wild type nucleotide sequence (thus a wild type amino acid sequence for fusion proteins) or as a mutant sequence bearing either the Ala285Val mutation, or the Leu286Val mutation, or the Leu392Val mutation. This was accomplished by recovering wild type or mutant sequence from appropriate sources of RNA using the oligonucleotide primers 989: ggatccggtccacttcgtatgctg, SEQ ID NO:141, and 990: ttttttgaattcttaggctatggttgtgttcca, SEQ ID NO:142. This allows cloning of the appropriate mutant or wild type nucleotide sequence corresponding to the hydrophilic acid loop domain at the BamHI and the EcoRI sites within the pGEX-KG vector.

These prokaryotic expression systems allow the holo-protein or various important functional domains of the protein to be recovered as fusion proteins and then used for binding studies, structural studies, functional studies, and for the generation of appropriate antibodies.

Expression of the ARMP gene in heterologous cell systems can be used to demonstrate structure-function relationships. Ligating the ARMP DNA sequence into a plasmid expression vector to transfect cells is a useful method to test the proteins influence on various cellular biochemical parameters. Plasmid expression vectors containing either the entire, normal or mutant human or mouse ARMP sequence or portions thereof, can be used in vitro mutagenesis experiments which will identify portions of the protein crucial for regulatory function.

The DNA sequence can be manipulated in studies to understand the expression of the gene and its product, to achieve production of large quantities of the protein for functional analysis, for antibody production, and for patient therapy. The changes in the sequence may or may not alter the expression pattern in terms of relative quantities, tissue-specificity and functional properties. Partial or full-length DNA sequences which encode for the ARMP protein, modified or unmodified, may be ligated to bacterial expression vectors. *E. coli* can be used using a variety of expression vector systems, e.g., the T7 RNA polymerase/promoter system using two plasmids or by labeling of plasmid-encoded proteins, or by expression by infection with M13 Phage mGPI-2. *E. coli* vectors can also be used with Phage lamba regulatory sequences, by fusion protein vectors (e.g. lacZ and trpE), by maltose-binding protein fusions, and by glutathione-S-transferase fusion proteins, etc., all of which together with many other prokaryotic expression systems are widely available commercially.

Alternatively, the ARMP protein can be expressed in insect cells using baculoviral vectors, or in mammalian cells using vaccinia virus or specialized eukaryotic expression vectors. For expression in mammalian cells, the cDNA sequence may be ligated to heterlogous promoters, such as the simian varus (SV40) promoter in the pSV2 vector and other similar vectors and introduced into cultured eukaryotic cells, such as COS cells to achieve transient or long-term expression. The stable integration of the chimeric gene construct may be maintained in mammalian cells by biochemical selection, such as neomycin and mycophoenolic acid.

The ARMP DNA sequence can be altered using procedures such as restriction enzyme digestion, fill-in with DNA polymerase, deletion by exonuclease, extension by terminal deoxynucleotide transferase, ligation of synthetic or cloned DNA sequences and site-directed sequence alteration with the use of specific oligonucleotides together with PCR.

The cDNA sequence or portions thereof, or a mini gene consisting of a cDNA with an introl and its own promoter, is introduced into eukaryotic expression vectors by conventional techniques. These vectors permit the transcription of the cDNA in eukaryotic cells by providing regulatory sequences that initiate and enhance the transcription of the cDNA and ensure its proper splicing and polyadenylation. The endogenous ARMP gene promoter can also be used. Different promoters within vectors have different activities which alters the level of expression of the cDNA. In addition, certain promoters can also modulate function such as the glucocorticoid-responsive promoter from the mouse mammary tumor virus.

Some of the vectors listed contain selectable markers or neo bacterial genes that permit isolation of cells by chemical selection. Stable long-term vectors can be maintained in cells as episomal, freely replicating entities using regulatory elements of viruses. Cell lines can also be produced which have integrated the vector into the genomic DNA. In this manner, the gene product is produced on a continuous basis.

Vectors are introduced into recipient cells by various methods including calcium phosphate, strontium phosphate, electroporation, lipofection, DEAE dextran, microinjection, or by protoplast fusion. Alternatively, the cDNA can be introduced by infection using viral vectors.

Using the techniques mentioned, the expression vectors containing the ARMP gene or portions thereof can be introduced into a variety of mammalian cells from other species or into non-mammalian cells.

The recombinant cloning vector, according to this invention, comprises the selected DNA of the DNA sequences of this invention for expression in a suitable host. The DNA is operatively linked in the vector to an expression control sequence in the recombinant DNA molecule so that normal and mutant ARMP protein can be expressed. The expression control sequence may be selected from the group consisting of sequences that control the expression of genes of prokaryotic or eukaryotic cells and their viruses and combinations thereof. The expression control sequence may be selected from the group consisting of the lac system, the trp system, the tac system, the trc system, major operator and promoter

regions of phage lambda, the control region of the fd coat protein, early and late promoters of SV40, promoters derived from polyoma, adenovirus, retrovirus, baculovirus, simian virus, 3-phosphoglycerate kinase promoter, yeast acid phosphatase promoters, yeast alpha-mating factors and combinations thereof.

The host cell which may be transfected with the vector of this invention may be selected from the group consisting of *E. coli, pseudomonas, bacillus subtillus, bacillus stearothermophilus*, or other bacili; other bacteria, yeast, fungi, insect, mouse or other animal, plant hosts, or human tissue cells.

For the mutant ARMP DNA sequence similar systems are employed to express and produce the mutant protein.

Antibodies to Detect ARMP

Antibodies to epitopes with the ARMP protein can be raised to provide information on the characteristics of the proteins. Generations of antibodies would enable the visualizations of the proteins in cells and tissues using Western blotting. In this technique, proteins are run on polyacrylamide gel and then transferred onto nitrocellulose membranes. These membranes are then incubated in the presence of the antibody (primary), then following washing are incubated to a secondary antibody which is used for detection of the protein-primary antibody complex. Following repeated washing, the entire complex is visualized using colourimetric or chemiluminescent methods.

Antibodies to the ARMP protein also allow for the use of immunocytochemistry and immunofluorescence techniques in which the proteins can be visualized directly in cells and tissues. This is most helpful in order to establish the subcellular location of the protein and the tissue specificity of the protein.

In order to prepare polyclonal antibodies, fusion proteins containing defined portions or all of the ARMP protein can be synthesized in bacteria by expression of corresponding DNA sequences in a suitable cloning vehicle. The protein can then be purified, coupled to a carrier protein and mixed with Freund's adjuvant (to help stimulate the antigenic response by the rabbits) and injected into rabbits or other laboratory animals. Alternatively, protein can be isolated from cultured cells expressing the protein. Following booster injections at bi-weekly intervals, the rabbits or other laboratory animals are then bled and the sera isolated. The sera can be used directly or purified prior to use, by various methods including affinity chromatography, Protein A-Sepharose, Antigen Sepharose, Anti-mouse-Ig-Sepharose. The sera can then be used to probe protein extracts run on a polyacrylamide gel to identify the ARMP protein. Alternatively, synthetic peptides can be made to the antigenic portions of the protein and used to inoculate the animals.

To produce monoclonal ARMP antibodies, cells actively expressing the protein are cultured or isolated from tissues and the cell membranes isolated. The membranes, extracts or recombinant protein extracts, containing the ARMP protein, are injected in Freund's adjuvant into mice. After being injected 9 times over a three week period, the mice spleens are removed and resuspended in a phosphate buffered saline (PBS). The spleen cells serve as a source of lymphocytes, some of which are producing antibody of the appropriate specificity. These are then fused with a permanently growing myeloma partner cell, and the products of the fusion are plated into a number of tissue culture wells in the presence of a selective agent such as HAT. The wells are then screened to identify those containing cells making useful antibody by ELISA. These are then freshly plated. After a period of growth, these wells are again screened to identify antibody-producing cells. Several cloning procedures are carried out until over 90% of the wells contain single clones which are positive for antibody production. From this procedure a stable line of clones is established which produce the antibody. The monoclonal antibody can then be purified by affinity chromatography using Protein A Sepharose, ion-exchange chromatography, as well as variations and combinations of these techniques.

In situ hybridization is another method used to detect the expression of ARMP protein. In situ hybridization relies upon the hybridization of a specifically labeled nucleic acid probe to the cellular RNA in individual cells or tissues. Therefore, it allows the identification of mRNA within intact tissues, such as the brain. In this method, oligonucleotides corresponding to unique portions of the ARMP gene are used to detect specific mRNA species in the brain.

In this method a rat is anesthetized and transcardially perfused with cold PBS, followed by perfusion with a formaldehyde solution. The brain or other tissues is then removed, frozen in liquid nitrogen, and cut into thin micron sections. The sections are placed on slides and incubated in proteinase K. Following rinsing in DEP, water and ethanol, the slides are placed in prehybridization buffer. A radioactive probe corresponding to the primer is made by nick translation and incubated with the sectioned brain tissue. After incubation and air drying, the labeled areas are visualized by autoradiography. Dark spots on the tissue sample indicate hybridization of the probe with brain mRNA which demonstrates the expression of the protein.

Antibodies may also be used coupled to compounds for diagnostic and/or therapeutic uses such as radionuclides for imaging and therapy and liposomes for the targeting of compounds to a specific tissue location.

Isolation and Purification of E5-1 Protein

The E5-1 protein may be isolated and purified by the types of methods described above for the ARMP protein.

The protein may also be prepared by expression of the E5-1 cDNA described herein in a suitable host. The protein is a preferably expressed as a fusion protein by ligating its encoding cDNA sequence to a vector containing the coding sequence for another suitable peptide, e.g., GST. The fusion protein is expressed and recovered from prokaryotic cells such as bacterial or baculovirus cells or from eukaryotic cells. Antibodies to ARMP, by virtue of portions of amino acid sequence identity with E5-1, can be used to purify, attract and bind to E5-1 protein and vice versa.

Transgenic Mouse Model of E5-1 Related Alzheimer's Disease

An animal model of Alzheimer's Disease related to mutations of the E5-1 gene may be created by methods analogous to those described above for the ARMP gene.

Antibodies

Due to its structural similarity with the ARMP, the E5-1 protein may be used for the development of probes, peptides, or antibodies to various peptides within it which may recognize both the E5-1 and the ARMP gene and gene products, respectively. As a protein homologue for the ARMP, the E5-1 protein may be used as a replacement for a defective ARMP gene product. It may also be used to elucidate functions of the ARMP gene in tissue culture and vice versa.

Screening for Alzheimer's Disease Linked to Chromosome 1

Screening for Alzheimer's Disease linked to mutations of the E5-1 gene may now be conveniently carried out.

General screening methods are described above in relation to the described mutations in the ARMP gene. These

described methods can be readily applied and adapted to detection of the described chromosome 1 mutations, as will be readily understood by those skilled in the art.

In accordance with one embodiment of the invention, the Asn141Ile mutation is screened for by PCR amplification of the surrounding DNA fragment using the primers:

1041: 5'-cattcactgaggacacacc (end-labelled) SEQ ID NO:163 and

1042: 5'-tgtagagcaccaccaaga (unlabelled) SEQ ID NO:164.

Any tissue with nucleated cell may be examined. The amplified products are separated by electrophoresis and an autoradiogram of the gel is prepared and examined for mutant bands.

In accordance with a further embodiment, the Met239Val mutation is screened for by PCR amplification of its surrounding DNA fragment using the primers:

1034: 5'-gcatggtgtgcatccact SEQ ID NO:165 and

1035: 5'-ggaccactctgggaggta SEQ ID NO:166.

The amplified products are separated and an autoradiogram prepared as described above to detect mutant bands.

The same primer sets may be used to detect the mutations by means of other methods such as SSCP, chemical cleavage, DGGE, nucleotide sequencing, ligation chain reaction and allele specific oligonucleotides. As will be understood by those skilled in the art, other suitable primer pairs may be devised and used.

In inherited cases, as the primary event, and in non-inherited cases as a secondary event due to the disease state, abnormal processing of E5-1, ARMP, APP or proteins reacting with E5-1, APP or ARMP, may occur. This can be detected as abnormal phosphorylation, glycoslyation, glycation amidation or proteolytic cleavage products in body tissues or fluids, e.g., CSF or blood.

Therapies

An important aspect of the biochemical studies using the genetic information of this invention is the development of therapies to circumvent or overcome the ARMP gene defect, and thus prevent, treat, control serious symptoms or cure the disease. In view of expression of the ARMP gene in a variety of tissues, one has to recognize that Alzheimer's Disease may not be restricted to the brain. Alzheimer's Disease manifests itself as a neurological disorder which in one of its forms is caused by a mutation in the ARMP gene, but such manifest may be caused by mutations in other organ tissues, such as the liver, releasing factors which affect the brain activity and ultimately cause Alzheimer's Disease. Hence, in considering various therapies, it is understood that such therapies may be targeted at tissue other than the brain, such as heart, placenta, lung, liver, skeletal muscle, kidney and pancreas, where ARMP is also expressed.

The effect of these mutations in E5-1 and ARMP is a gain of novel function which causes aberrant processing of (APP) Amyloid Precursor Protein into Aβ peptide, abnormal phosphorylation homeostasis, and abnormal apoptosis. Therapy to reverse this will be small molecules (drugs) recombinant proteins, etc. which block the aberrant function by altering the structure of the mutant proteins, etc. which block the aberrant function by altering the structure of the mutant protein, enhancing its metabolic clearance or inhibiting binding of ligands to the mutant protein, enhancing its metabolic clearance or inhibiting binding of ligands to the mutant protein, or inhibiting the channel function of the mutant protein. The same effect might be gained by inserting a second mutant protein by gene therapy similar to the correction of the "Deg 1(d)" and "Mec 4(d)" mutations in *C. elegans* by insertion of mutant transgenes. Alternatively over expression of wild type E5-1 protein or wild type ARMP or both may correct the defect. This could be the administration of drugs or proteins to induce the transcription and translation or inhibit the catabolism of the native E5-1 and ARMP proteins. It could also be accomplished by infusion of recombinant proteins or by gene therapy with vectors causing expression of the normal protein at a high level.

Rationale for Therapeutic, Diagnostic, and Investigational Applications of the ARMP Gene and Gene Products as they Relate to the Amyloid Precursor Protein

The Aβ peptide derivatives of APP are neurotoxic (Selkoe et al, 1994). APP is metabolized by passages through the Golgi network and then to secretory pathways via clathrin-coated vesicles with subsequent passage to the plasma membrane where the mature APP is cleaved by α-secretase to a soluble fraction (Protease Nexin II) plus a non-amyloidogenic C-terminal peptide (Selkoe et al. 1995, Gandy et al., 1993). Alternatively, mature APP can be directed to the endosome-lysosome pathway where it undergoes beta and gamma secretase cleavage to produce the Aβ peptides. The phosphorylation state of the cell determines the relative balance of α-secretase (non-amyloidogenic) or Aβ pathways (amyloidogenic pathway) (Gandy et al., 1993). The phosphorylation state of the cell can be modified pharmacologicially by phorbol esters, muscarinic agonists and other agents, and appears to be mediated by cytosolic factors (especially protein kinase C) acting upon an integral membrane protein in the Golgi network, which we propose to the ARMP, and members of the homologous family (all of which carry several phosphorylation consensus sequences for protein kinease C). Mutations in the ARMP gene will cause alterations in the structure and function of the ARMP gene product leading to defective interactions with regulatory elements (e.g., protein kinase C) or with APP, thereby promoting APP to be directed to the amyloidogenic endosome-lysosome pathway. Environmental factors (viruses, toxins, and aging, etc.) may also have similar effects on ARMP. To treat Alzheimer's Disease, the phosphorylation state of ARMP can be altered by chemical and biochemical agents (e.g. drugs, peptides and other compounds) which alter the activity of protein kinase C and other protein kinase, or which alter the activity of protein phosphatases, or which modify the availability of ARMP to be postranslationally modified. The interactions between kinases and phosphatases with the ARMP gene products (and the products of its homologues), and the interactions of the ARMP gene products with other proteins involved in the trafficking of the APP within the Golgi network can be modulated to decrease trafficking of Golgi vesicles to the endosome-lysosome pathway thereby promoting Aβ peptide production. Such compounds will include: peptide analogues of APP, ARMP, and homologues of ARMP as well as other interacting proteins, lipids, sugars, and agents which promote differential glycosylation of ARMP and its homologues; agents which alter the biologic half-life of messenger RNA or protein of ARMP and homologues including antibodies and antisense oligonucleotides; and agents which act upon ARMP transcription.

The effect of these agents in cell lines and whole animals can be monitored by monitoring: transcription; translation; post-translational modification of ARMP (e.g., phosphorylation or glycoslyation); and intracellular trafficking of ARMP and its homologues through various intracellular and extracellular compartments. Methods for these studies include Western and Northern blots; immunoprecipitation after metabolic labeling (pulse-chase) with radio-labeled methionine

and ATP, and imminohistochemistry. The effect of these agents can also be monitored using studies which examine the relative binding affinities and relative amounts of ARMP gene products in interactions with protein kinase C and/or APP using either standard binding affinity assays or co-precipitation and Western blots using antibodies to protein kinase C, APP or ARMP and its homologues. The effect of these agents can also be monitored by assessing the production of Aβ peptides by ELISA before and after exposure to the putative therapeutic agent (Huang et al., 1993). The effect can also be monitored by assessing the viability of cell lines after exposure to aluminum salts and to Aβ peptides which are through to be neurotoxic in Alzheimer's Disease. Finally, the effect of these agents can be monitored by assessing the cognitive function of animals bearing: their normal genotype at APP or ARMP homologues; bearing human APP transgenes (with or without mutations); or bearing human ARMP transgenes (With or without mutations); or a combination of all of these.

Rationale for Therapeutic, Diagnostic, and Investigational Applications of the ARMP Gene, the E5-1 Gene and Their Products

The ARMP gene product and the E5-1 gene product have amino acid sequence homology to human ion channel proteins and receptors. For instance, the E5-1 protein shows substantial homology to the human sodium channel α-subunit (E=0.18, P=0.16, identities=22-27% over two regions of at least 35 amino acid residues) using the BLASTP paradigm of Atschul et al. 1990. Other diseases (such as malignant hyperthermia and hyperkalemic periodic paralysis in humans and the neurodegenerative of mechanosensory neurons in *C. elegans*) arise through mutations in ion channels or receptor proteins. Mutation of the ARMP gene or the E5-1 gene could affect similar functions and lead to Alzheimer's Disease and other psychiatric and neurological diseases. Based upon this, a test for Alzheimer's Disease can be produced to detect an abnormal receptor or an abnormal ion channel function related to abnormalities that are acquired or inherited in the ARMP gene and its product or in one of the homologous genes such as E5-1 and their products. This test can be accomplished either in vivo or in vitro by measurements of ion channel fluxes and/or transmembrane voltage or current fluxes using patch clamp, voltage clamp and fluorescent dyes sensitive to intracellular calcium or transmembrane voltage. Defective ion channel or receptor function can also be assayed by measurements of activation of second messengers such as cyclic AMP, cGMP tyrosine kinases, phosphates, increases in intracellular Ca^{2+} levels, etc. Recombinantly made proteins may also be reconstrued in artificial membrane systems to study ion channel conductance. Therapies which affect Alzheimer's Disease (due to acquired/inherited defects in the ARMP gene or E5-1 gene; due to defects in other pathways leading to this disease such as mutations in APP; and due to environmental agents) can be tested by analysis of their ability to modify an abnormal ion channel or receptor function induced by mutation in the ARMP gene or in one of its homologues. Therapies could also be tested by their ability to modify the normal function of an ion channel or receptor capacity of the ARMP gene products and its homologues. Such assays can be performed on cultured cells expressing endogenous normal or mutant ARMP genes/gene products or E5-1 genes/gene products. Such studies can be performed in addition on cells transfected with vectors capable of expressing ARMP, parts of the ARMP gene and gene product, mutant ARMP, E5-1 gene, parts of the E5-1 gene and gene product, mutant E5-1 gene or another homologue in normal or mutant form. Therapies for Alzheimer's Disease can be devised to modify an abnormal ion channel or receptor function of the ARMP gene or E5-1 gene. Such therapies can be conventional drugs, peptides, sugars, or lipids, as well as antibodies or other ligands which affect the properties of the ARMP or E5-1 gene product. Such therapies can also be performed by direct replacement of the ARMP gene and/or E5-1 gene by gene therapy. In the case of an ion channel, the gene therapy could be performed using either mini-genes (cDNA plus a promoter) or genomic constructs bearing genomic DNA sequences for parts or all of the ARMP gene. Mutant ARMP or homologous gene sequence might also be used to counter the effect of the inherited or acquired abnormalities of the ARMP gene as has recently been done for replacement of the mec 4 and deg 1 in *C. elegans* (Huang and Chalfie, 1994). The therapy might also be directed at augmenting the receptor or ion channel function of the homologous genes such as the E5-1 gene, in order that it may potentially take over the functions of the ARMP gene rendered defective by acquired or inherited defects. Therapy using antisense oligonucleotides to block the expression of the mutant ARMP gene or the mutant E5-1 gene, coordinated with gene replacement with normal ARMP or E5-1 gene can also be applied using standard techniques of either gene therapy or protein replacement therapy.

Protein Therapy

Treatment of Alzheimer's Disease can be performed by replacing the mutant protein with normal protein, or by modulating the function of the mutant protein. Once the biological pathway of the ARMP protein has been completely understood, it may also be possible to modify the pathophysiologic pathway (e.g., a signal transduction pathway) in which the protein participates in order to correct the physiological defect.

To replace the mutant protein with normal protein, or with a protein bearing a deliberate counterbalancing mutation it is necessary to obtain large amounts of pure ARMP protein or E5-1 protein from cultured cell systems which can express the protein. Delivery of the protein to the affected brain areas or other tissues can then be accomplished using appropriate packaging or administrating systems.

Gene Therapy

Gene therapy is another potential therapeutic approach in which normal copies of the ARMP gene are introduced into patients to successfully code for normal protein in several different affected cell types. The gene must be delivered to those cells in a form in which it can be taken up and code for sufficient protein to provide effective function. Alternatively, in some neurologic mutants it has been possible to prevent disease by introducing another copy of the homologous gene bearing a second mutation in that gene or to alter mutation, or use another gene to block its effect.

Retroviral vectors can be used for somatic cell gene therapy especially because of their high efficiency of infection and stable integration and expression. The targeted cells however must be able to divide and the expression of the levels of normal protein should be high because the disease is a dominant one. The full length ARMP gene can be cloned into a retroviral vector and driven from its endogenous promoter or from the retroviral long terminal repeat or from a promoter specific for the target cell type of interest (such as neurons).

Other viral vectors which can be used include adeno-associated virus, vaccinia virus, bovine papilloma virus, or a herpesvirus such as Epstein-Barr virus.

Gene transfer could also be achieved using non-viral means requiring infection in vitro. This would include cal-

cium phosphate, DEAE dextran, electroporation, and protoplast fusion. Liposomes may also be potentially beneficial for delivery of DNA into a cell. Although these methods are available, many of these are lower efficiency.

Antisense based strategies can be employed to explore ARMP gene function and as a basis for therapeutic drug design. The principle is based on the hypothesis that sequence-specific suppression of gene expression can be achieved by intracellular hybridization between mRNA and a complementary antisense species. The formation of a hybrid RNA duplex may then interfere with the processing/transport/translation and/or stability of the target ARMP mRNA. Hybridization is required for the antisense effect to occur, however the efficiency of intracellular hybridization is low and therefore the consequences of such an event may not be very successful. Antisense strategies may use a variety of approaches including the use of antisense oligonucleotides, injection of antisense RNA and transfection of antisense RNA expression vectors. Antisense effects can be induced by control (sense) sequences, however, the extent of phenotypic changes are highly variable. Phenotypic effects induced by antisense effects are based on changes in criteria such as protein levels, protein activity measurement, and target mRNA levels. Multidrug resistance is a useful model to study molecular events associated with phenotypic changes due to antisense effects, since the multidrug resistance phenotype can be established by expression of a single gene mdrl (MDR gene) encoding for P-glycoprotein.

Transplantation of normal genes into the affected area of the patient can also be useful therapy for Alzheimer's Disease. In this procedure, a normal hARMP protein is transferred into a cultivable cell type such as glial cells, either exogenously or endogenously to the patient. These cells are then injected serotologicially into the disease affected tissue(s). This is a known treatment for Parkinson's disease.

Immunotherapy is also possible for Alzheimer's Disease. Antibodies can be raised to a mutant ARMP protein (or portion thereof) and then administered to bind or block the mutant protein and its deliterious effects. Simultaneously, expression of the normal protein product could be encouraged. Administration could be in the form of a one time immunogenic preparation or vaccine immunization. An immunogenic composition may be prepared as injectables, as liquid solutions or emulsions. The ARMP protein may be mixed with pharmaceutically acceptable excipients compatible with the protein. Such excipients may include water, saline, dextrose, glycerol, ethanol and combinations thereof. The immunogenic composition and vaccine may further contain auxiliary substances such as emulsifying agents or adjuvants to enhance effectiveness. Immunogenic compositions and vaccines may be administered parenterally by injection subcutaneously or intramuscularly.

The immunogenic preparations and vaccines are administered in such amount as will be therapeutically effective, protective and immunogenic. Dosage depends on the route of administration and will vary according to the size of the host.

Similar gene therapy techniques may be employed with respect to the E5-1 gene.

The above disclosure generally describes the present invention. A more complete understanding can be obtained by reference to the following specific examples. These examples are described solely for purposes of illustration and are not intended to limit the scope of the invention. Changes in the form and substitution of equivalents are contemplated as circumstances may suggest or render expedient. Although specific terms have been employed herein, such terms are intended in a descriptive sense and not for purposes of limitations.

EXAMPLE 1

Development of the Genetic, Physical "contig" and Transcriptional Map of the Minimal Co-Segregating Region

The CEPH Mega YAC and the RPCI PAC human total genomic DNA libraries were searched for clones containing genomic DNA fragments from the AD3 region of chromosome 14q24.3 using oliginucleotide probes for each of the ## SSR marker loci used in the genetic linkage studies as well as ## additional markers depicted in FIG. **1***a* (Albertsen et al., 1990; Chumakov et al., 1992; Ioannu et al., 1994). The genetic map distances between each marker are depicted above the contig, and are derived from published data (NIH/CEPH Collaborative Mapping Group, 1992; Wang, 1992; Weissenbach, J. et al., 1992 ; Gyapay, G. et al., 1994). Clones recovered for each of the initial marker loci were arranged into an ordered series of partially overlapping clones ("contig") using four independent methods. First, sequences representing the ends of the YAC insert were isolated by inverse PCR (Riley et al., 1990), and hybridized to Southern blot panels containing restriction digests of DNA from all of the YAC clones bearing overlapping sequences. Second, inter-Alu PCR was performed on each YAC, and the resultant band patterns were compared across the pool of recovered YAC clones in order to identify other clones bearing overlapping sequences (Bellamne-Chartelot et al., 1992; Chumakov et al; 1992). Third, to improve the specificity of the Alu-PCR fingerprinting, we restricted the YAC DNA with HaeIII or RsaI, amplified the restriction products with both Alu and LlH consensus primers, and resolved the products by polyacrylamide gel electrophoresis. Finally, as additional STSs were generated during the search for transcribed sequences, these STSs were also used to identify overlaps. The resultant contig was complete except for a single discontinuity between YAC932C7 bearing D14S53 and YAC746B4 containing D14S61. The physical map order of the STSs within the contig was largely in accordance with the genetic linkage map for this region (NIH/CEPH Collaborative Mapping Group, 1992; Wang, Z., Webber, J. L., 1992; Weissenbach, J. et al., 1992; Gyapay, G. et al., 1994). However, as with the genetic maps, we were unable to unambiguously resolve the relative order of the loci within the D14S43/D14S71 cluster and the D14S76/D14S273 cluster. PAC1 clones suggest that D14S277 is telomeric to D14S268, whereas genetic maps have suggested the reverse order. Furthermore, a few STS probes failed to detect hybridization patterns in at least one YAC clone which, on the basis of the most parsimonious consensus physical map and from the genetic map, would have been predicted to contain that STS. For instance, the D14S268 (AFM265) and RSCAT7 STSs are absent from YAC788H12 . Because these results are reproducible, and occurred with several different STS markers, these results most likely reflect the presence of small interstitial deletions with one of the YAC clones.

EXAMPLE 2

Cumulative Two-point Lod Scores for Chromosome 14q24.3 Markers

Genotypes of each polymorphic microsatellite marker locus were determined by PCR from 1000 ng of genomic

DNA of all available affected and unaffected pedigree members as previously described (St. George-Hyslop, P et al, 1992) using primer sequences specific for each microsatellite locus (Weissenbach, J et al., 1992; Gyapay, G et al., 1994). The normal population frequency of each allele was determined using spouses and other neurologically normal subjects from the same ethnic groups, but did not differ significantly from those established for mixed Caucasian populations (Weissenbach, J. et al., 1992; Gyapay, G. et al., 1994). The maximum likelihood calculations assumed an age of onset correction, marker allele frequencies derived from published series of mixed Caucasian subjects, an estimated allele frequence for the AD3 mutation of 1:1000 as previously described (St. George-Hyslop, P. et al., 1992). The analyses were repeated using equal marker allele frequencies, and using phenotype information only from affected pedigree members as previously described to ensure that inaccuracies in the estimated parameters used in the maximum likelihood calculations did not misdirect the analyses (St. George-Hyslop, P. et al., 1992). These supplemental analyses did not significantly alter either the evidence supporting linkage, or the discovery of recombination events.

EXAMPLE 3

Haplotypes Between Flanking Markers Segregated with AD3 in FAD Pedigrees

Extended haplotypes between the centromeric and telomeric flanking markers on the parental copy of chromosome 14 segregating with AD3 in fourteen early onset FAD pedigrees (pedigrees NIH2, MGH1, Tor1.1, FAD4, FAD1, MEX1, and FAD2 show pedigree specific lod scores ≧+3.00 with at least one marker between D14S258 and D14S53). Identical partial haplotypes (boxed) are observed in two regions of the disease bearing chromosome segregating in several pedigrees of similar ethnic origin. In region A, shared alleles are seen at D14S268 ("B": allele size=126 bp, allele frequence in normal Caucasians=0.04; "C": size=124 bp, frequency=0.38); D14S277 ("B": size=156 bp, frequency=0.19; "C": size—154 bp, frequency=0.33); and RSCAT6 ("D": size=111 bp, frequency 0.25; "E" size=109 bp, frequency=0.20; "F" size=107 bp, frequency=0.47). In region B, alleles of identical size are observed at D14S43 ("A": size=193 bp, frequency=0.01; "D": size 187 bp, frequency=0.12; "E" size=185 bp, frequency=0.26; "I" size=160 bp, frequency=0.38); D14S273 ("3": size=193 bp, frequency=0.38; "4" size=191 bp, frequency=0.16; "5": size=189 bp, frequency=0.34; "6": size=187 bp, frequency=0.02) and D14S76 ("1": size=bp, frequency=0.01; "5": size=bp, frequency=0.38; "6": size=bp, frequency=0.07, "9": size=bp, frequency=0.38). The ethnic origins of each pedigree are abbreviated as: Ashk=Askenazi Jewish; Ital=Southern Italian; Angl=Anglo-Saxon-Celt; FrCan=French Canadian; Jpn=Japanese; Mex=Mexican Caucasian; Ger=German; Am=American Caucasian. The type of mutation detected is depicted by the amino acid substitution and putative condon number or by ND where no mutation has been detected because a comprehensive survey has not been undertaken due to the absence of a source of mRNA for RT-PCR studies.

EXAMPLE 4

Recovery of Transcribed Sequences from the AD3 Interval

Putative transcribed sequences encoded in the AD3 interval were recovered using either a direct hybridization method in which short cDNA fragments generated from human brain mRNA were hypridized to immobilized cloned genomic DNA fragments (Rommens, J M et al., 1993). The resultant short putatively transcribed sequences were used as probes to recover longer transcripts from human brain cDNA libraries (Stratagene, La Jolla). The physical locations of the original short clone and of the subsequently acquired longer cDNA clones were established by analysis of the hybridization pattern generated by hybridizing the probe to Southern blots containing a panel of EcoRI digested total DNA samples isolated from individual YAC clones within the contig. The nucleotide sequence of each of the longer cDNA clones was determined by automated cycle sequencing (Applied Biosystems Inc., CA), and compared to other sequences in nucleotide and protein databases using the blast algorithm (Atschul, S F et al., 1990). Accession numbers for the transcribed sequences in this report are L40391, L40392, L40393, L40394, L40395, L40396, L40397, L40398, L40399, L40400, L40401, L40402, and L40403.

EXAMPLE 5

Locating Mutations in the ARMP Gene Using Restriction Enzymes

The presence of Ala 246 Glu mutation which creates a DdeI restriction site was assayed in genomic DNA by PCR using the end labelled primer 849 (5'-atctccggcaggcatatct-3') SEQ ID NO:129 and the unlabelled primer 892 (5'-tgaaatcacagccaagatgag-3') SEQ ID NO:130 to amplify an 84 bp genomic exon fragment using 100 ng of genomic DNA template, 2 mM $MgCl_2$, 10 pMoles of each primer, 0.5 U Taq polymerase, 250 uM dNTPs for 30 cycles of 95° C.×20 seconds, 60° C.×20 seconds, 72° C.×5 seconds. The products were incubated with an excess of DdeI for 2 hours according to the manufacturers protocol, and the resulting restriction fragments were resolved on a 6% nondenaturing polyacrylamide gel and visualized by autoradiography. The presence of the mutation was inferred from the clevage of the 84 bp fragment due to the presence of a DdeI restriction site. All affected members of the FAD1 pedigree (filled symbols) and several at-risk members ("R") carried the DdeI site. None of the obligate escapees (those individuals who do not get the disease, age >70 years), and none of the normal controls carried the DdeI mutation.

EXAMPLE 6

Location Mutation in the ARMP Gene Using Allelle Specific Oligonucleotides

The presence of the Cys 410 Tyr mutation was assayed using allele specific oligonucleotides. 100 ng of genomic DNA was amplified with the exonic sequence primer 885 (5'-tggagactggaacacaac-3') SEQ ID NO:127 and the opposing intronic sequence primer 893 (5'-gtgtggccagggtagagaact-3') SEQ ID NO:128 using the above reaction conditions except 2.5 mM $MgCl_2$, and cycle conditions of 94° C.×20 seconds, 58° C.×20 seconds, and 72° C. for 10 seconds). The resultant 216 bp genomic fragment was denatured by 10-fold dilution in 0.4M NaOH, 25 mM EDTA, and was vacuum slot-blotted to duplicate nylon membranes. The end-labelled "wild-type" primer 890 (5'-ccatagcctgtttcgtagc-3') SEQ ID NO:131 and the end-labelled "mutant" primer 891 (5'-ccatagcctAtttcgtagc-3') SEQ ID NO:132 were hybridized to separate copies of the slot-blot filters in 5×SSC, 5× Denhardt's, 0.5% SDS for 1 hour at 48° C., and then washed successively in 2×SSC at 23° C. and 2×SSC, 0.1% SDS at 50° C. and then

exposed to X-ray film. All testable affected members as well as some at-risk members of the AD3 (shown) and NIH2 pedigrees (not shown) possessed the Cys 410 Tyr mutation. Attempts to detect the Cys 410 Try mutation by SSCP revealed that a common intronic sequence polymorphism migrated with the same SSCP pattern.

EXAMPLE 7

Northern Hybridization Demonstrating the Expression of ARMP Protein mRNA in a Variety of Tissues

Total cytoplasmic RNA was isolated from various tissue samples (including heart, brain, and different regions of placenta, lung, liver, skeletal muscle, kidney and pancreas) obtained from surgical pathology using standard procedures such as CsCl purification. The RNA was then electrophoresed on a formaldehyde gel to permit size fractionation. The nitrocellulose membrane was prepared and the RNA was then transferred onto the membrane. ^{32}P-labelled cDNA probes were prepared and added to the membrane in order for hybridization between the probe the RNA to occur. After washing, the membrane was wrapped in plastic film and placed into imaging cassettes containing X-ray film. The autoradiographs were then allowed to develop for one to several days. The positions of the 28S and 18S rRNA bands are indicated. Sizing was established by comparison to standard RNA markers. Analysis of the autoradiographs revealed a prominent band at 3.0 kb in size. These northern blots demonstrated the ARMP gene is expressed in all of the tissues examined.

EXAMPLE 8

Eukaryotic and Prokaryotic Expression Vector Systems

Eukaryotic and prokaryotic expression systems have been generated using two different classes of ARMP nucleotide cDNA sequence inserts. In the first class, termed full-length constructs, the entire ARMP cDNA sequence was inserted into the expression plasmid in the correct orientation, and included both the natural 5' UTR and 3' UTR sequences as well as the entire open reading frame. The open reading frames bear a nucleotide sequence cassette which allows either the wild type open reading frame to be included in the expression system or alternatively, single or a combination of double mutations can be inserted into the open reading frame. This was accomplished by removing a restriction fragment from the wild type open reading frame using the enzymes NarI and PflmI and replacing it with a similar fragment generated by reverse transcriptase PCR and which bears the nucleotide sequence encoding either the Met146Leu mutation or the Hys163Arg mutation. A second restriction fragment was removed from the wild type normal nucleotide sequence for the open reading frame by cleavage with the enzymes PflmI and NcoI and replaced with restriction fragments bearing either the nucleotide sequence encoding the Ala246Glu mutation, or the Ala260Val mutation or the Ala285Val mutation or the Leu286Val mutation, or the Leu392Val mutation, or the Cys410 Tyr mutation. Finally, a third variant bearing combinations of either the Met146Leu or His163Arg mutations in tandem with the remaining mutations by linking the NarI-PflmI fragment bearing these mutations and the PflmI-NcoI fragment bearing the remaining mutations.

A second variant of cDNA inserts bearing wild type or mutant cDNA sequences was constructed by removing from the full-length cDNA the 5' UTR and part of the 3' UTR sequences. The 5' UTR sequence was replaced with a synthetic oligonucleotide containing a KpnI restriction site and a Kozak initiation site (oligonucleotide 969: ggtaccgccaccatgacagaggtacctgcac) SEQ ID NO:139. The 3' UTR was replaced with an oligonucleotide corresponding to position 2566 of the cDNA and bears an artificial EcoRI site (oligonucleotide 970:gaattcactggctgtagaaaaagac) SEQ ID NO:140. Mutant variants of this construct were then made by inserting the same mutant sequences described above at the NarI-PflmI fragment, and at the PsImI-NcoI sites described above.

For eukaryotic expressions, these various cDNA constructs bearing wild type and mutant sequences were cloned into the expression vector pZeoSV (invitrogen). For prokaryotic expression, two constructs were made using the gluthathione S-transferase fusion vector pGEX-kg. The inserts which have been attached to the GST fusion nucleotide sequence are the same nucleotide sequence described above generated with the oligonucleotide primers 969, SEQ ID NO:139 and 970, SEQ ID NO:140, bearing either the normal open reading frame nucleotide sequence or bearing a combination of single and double mutations as described above. This construct allows expression of the full-length protein in mutant and wild type variants in prokaryotic cell systems as a GST fusion protein which will allow purification of the full-length protein followed by removal of the GST fusion product by thrombin digestion. The second prokaryotic cDNA construct was generated to create a fusion protein with the same vector, and allows the production of the amino acid sequence corresponding to the hydrophillic acid loop domains between TM6 and TM7 of the full-length protein, as either a wild type nucleotide sequence (thus a wild type amino acid sequence for fusion proteins) or as a mutant sequence bearing either the Ala285Val mutation, or the Leu286Val mutation, or the Leu392Val mutation. This was accomplished by recovering wild type or mutant sequence from appropriate sources of RNA using the oligonucleotide primers 989:ggatccggtccacttcgtatgctg SEQ ID NO:141, and 990:ttttttgaattcttaggctatggttgtgttcca SEQ ID NO:142. This allows cloning of the appropriate mutant or wild type nucleotide sequence corresponding to the hydrophillic acid loop domain at the BamHI and the EcoRI sites within the pGEX-KG vector.

These prokaryotic expression systems allow the holo-protein or various important functional domains of the protein to be recovered as fusion proteins and then used for binding studies, structural studies, functional studies, and for the generation of appropriate antibodies.

EXAMPLE 9

Identification of Three New Mutations in the ARMP Gene

Three novel mutations have been identified in subjects affected with early onset Alzheimer's Disease. All of these mutations co-segregate with the disease, and are absent from at least 200 normal chromosomes. The three mutations are as follows: a substitution of C by T at position 1027 which results in the substitution of alanine 260 for valine; substitution of C by T at position 1102, which results in the substitution of alanine at 285 by valine; and substitution of C by G at position 1422 which results in the substitution of leucine 392 by valine. Significantly, all of these mutations occur within the acidic hydrophillic loop between putative. TM6 and TM7. Two of the mutations (A260V; A285V) and the L286V mutation are also located in the alternative spliced domain.

The three new mutations, like the other mutations, can be assayed by a variety of strategies (direct nucleotide sequencing, Allele specific oligos, ligation polymerase chain reaction, SSCP, RFLPs) using RT-PCR products representing the mature mRNA/cDNA sequence or genomic DNA. We have chosen allele specific oligos. For the A260V and the A285V mutations, genomic DNA carrying the exon can be amplified using the same PCR primers and methods for the L286V mutation. PCR products were then denatured and slot blotted to duplicate nylon membranes using the slot blot protocol described for the C410T mutation.

The Ala260Val mutation was scored by these blots by using hybridization with end-labeled allele-specific oligonucleotides corresponding to the wild type sequence (994:gattagtggttgttttgtg) SEQ ID NO:143 or the mutant sequence (995: gattagtggctgttttgtg) SEQ ID NO:144 by hybridization at 48° C. followed by a wash at 52° in 3×SSC buffer containing 0.1% SDS. The Ala285Val mutation was scored on these slot blots as described above but using instead the allele-specific oligonucleotides for the wild type sequence (1003:tttttccagctctcattta) SEQ ID NO:145 or the mutant primer (1004: tttttccagttctcattta) SEQ ID NO:146 at 48° C. followed by washing at 52° C. as above except that the wash solution was 2×SSC.

The Leu392Val mutation was scored by amplification of the exon from genomic DNA using primers 996 (aaacttggattgggagat) SEQ ID NO:167 and 893 (gtgtggccagggtagagaact) SEQ ID NO:128 using standard PCR buffer conditions excepting that the magnesium concentration was 2 mM and cycle conditions were 94° C. time 10 seconds, 56° C. times 20 seconds, and 72° C. for 10 seconds. The result 200 based pair genomic fragment was denatured as described for the Cys410Tyr mutation and slot-blotted in duplicate to nylon membranes. The presence or absence of the mutation was then scored by differential hybridization to either a wild type end-labelled oligonucleotide (999:tacagtgttctggttggta) SEQ ID NO:148 or with an end-labeled mutant primer (100:tacagtgttgtggttggta) SEQ ID NO:149 by hybridization at 45° C. and then successive washing in 2×SSC at 23° and then at 68° C.

EXAMPLE 10

Polyclonal Antibody Production

Peptide antigens were synthesized by solid-phase techniques and purified by reverse phase high pressure liquid chromatography. Peptides were covalently linked to keyhole limpet hematoxylin (KLH) via disulfide linkages that were made possible by the addition of a cystein residue at the peptide C-terminus. This additional residue does not appear normally in the protein sequence and was included only to facilitate linkage to the KLH molecule. A total of three rabbits were immunized with peptide-KLH complexes for each peptide antigen and were then subsequently give booster injections at seven day intervals. Antisera were collected for each peptide and pooled and IgG precipitated with ammonium sulfate. Antibodies were then affinity purified with Sulfo-link agarose (Pierce) coupled with the appropriate peptide. This final purification is required to remove non-specific interactions of other antibodies present in either the pre- or post-immune serum.

The specific sequences to which we have raised antibodies are:

SEQ ID NO:168
Polyclonal antibody 1:
NDNRERQEHNDRRSL (C)-residues 30-44

SEQ ID NO:169
Polyclonal antibody 2:
KDGQLIYTPFTEDTE (C)-residues 109-123

SEQ ID NO:170
Polyclonal antibody 3:
EAQRRVSKSKYNAE (C)-residues 304-318

SEQ ID NO:171
Polyclonal antibody 4:
SHLGPHRSTPESRAA (C)-residues 346-360

The non-native cysteine residue is indicated at the C-terminal by (C). These sequences are contained within various predicted domains of the protein. For example, antibodies 1, 3, and 4 are located in potentially functional domains that are exposed to the aqueous media and may be involved in binding to other proteins critical for the development of the disease phenotype. Antibody 2 corresponds to a short linking region situated between the predicted first and second transmembrane helices.

EXAMPLE 11

Identification of Two Mutations in E5-1 Gene

RT-PCR products corresponding to the E5-1 ORF were generated from RNA of lymphoblasts or frozen post-mortem brain tissue using oligonucleotide primer pairs 1021:5'-cagaggatggagagaatac SEQ ID NO:172 and 1018:5'-ggctccccaaaactgtcat SEQ ID NO:173 (product=888 bp); and 1071: 5'-gccctagtgttcatcaagta SEQ ID NO:174 and 1022:5'-aaagcgggagccaaagtc SEQ ID NO:175 (product=826 bp) by PCR using 250 μMol dNTPs, 2.5 mM MgCl2, 10 pMol oligunucleotides in 10 μl cycled for 40 cycles of 94° C.×20 seconds, 58° C.×20 seconds, 72° C.×45 seconds. The PCR products were sequenced by automated cycle sequencing (ABI, Foster City, A) and the fluorescent chromatograms were scanned for heterozygous nucleotide substitutions by direct inspection and by the Factura (ver 1.2.0) and Sequence Navigator (ver 1.0.1b15) software packages (data not shown).

Asn141Ile: the A→T substitution at nucleotide 787 creates a Bc1I restriction site. The exon bearing this mutation was amplified from 100 ng of genomic DNA using 10 pMol of oligonucleotides 1041: 5'-cattcactaggacacacc SEQ ID NO:163 (end-labelled) and 1042: 5'-tgtagagcaccaccaaga SEQ ID NO:164 (unlabelled), and PCR reaction conditions similar to those described below for the Met239Val. 2 μl of the PCR product was restricted to Bc1I (NEBL, Beverly, Mass.) in 10 μl reaction volume according to the manufacturers' protocol, and the products were resolved by non-denaturing polyacrylamide gel electrophoresis. In subjects with wild type sequences, the 114 bp PCR product is cleaved into 68 bp and 46 bp fragments. Mutant sequences cause the product to be cleaved into 53 bp, 46 bp and 15 bp.

Met239Val: The A→G substitution at nucleotide 1080 deletes a NlaIII restriction site, allowing the presence of the Met239Val mutation to be detected by amplification from 100 ng of genomic DNA using PCR (10 pMol oligonucleotides 1034:5'-gcatggtgtgcatccact SEQ ID NO:165, 1035:5'-ggaccactctgggaggta SEQ ID NO:166; 0.5 U Taq polymerase, 250 μM dNTPS, 1 μCi alpha ^{32}P-dCTP, 1.5 mM $MgCI_2$, 10 μl

volume; 30 cycles of 94° C.×30 seconds, 58° C.×20 seconds, 72° C.×20 seconds) to generate a 110 bp product. 2 μl of the PCR reaction were diluted to 10 μl and restricted with 3 U of NlaIII (NEBL, Beverly Mass.) for 3 hours. The restriction products were resolved by non-denaturing polyacrylamide gel electrophoresis and visualized by autoradiography. Normal subjects show cleavage products of 55, 35, 15 and 6 bp, whereas the mutant sequence gives fragments of 55, 50 and 6 bp.

Although preferred embodiments of the invention have been described herein in detail, it will be understood by those skilled in the art that variations may be made thereto without departing from the spirit of the invention or the scope of the appended claims.

TABLE 1

	RECOMBINATION FRACTION (θ)						
LOCUS	0.00	0.05	0.10	0.15	0.20	0.30	0.40
D14S63	−∞	1.54	3.90	4.38	4.13	2.71	1.08
D14S258	−∞	21.60	19.64	17.19	14.50	8.97	3.81
D14S77	−∞	15.18	15.53	14.35	12.50	7.82	2.92
D14S71	−∞	15.63	14.14	12.19	10.10	5.98	2.39
D14S43	−∞	19.36	17.51	15.27	12.84	7.80	3.11
D14S273	−∞	12.30	11.52	10.12	8.48	5.04	1.91
D14S61	−∞	26.90	24.92	22.14	18.98	12.05	5.07
D14S53	−∞	11.52	11.41	10.39	8.99	5.73	2.51
D14S48	−∞	0.50	1.05	1.14	1.04	0.60	0.18

TABLE 2

	PEDIGREE ID													
LOCUS	N1B2	FaD3	TUR1.1	FaD4	RB	FaD1	BIG12	BOW	COOK	603	Tor42	QUE	MEX1	FAD2
D14S83	1	4	7	4		5							9	2
D14S258	6	6	8	7	4	5	5	6	6		7	6	7	6
D14S268	C	C	B	B	C	C	C	C	C	C	C	B	C	C
D14S277	C	C	C	C	C	C	C	C	C	A	A	C	B	
D14S786	D	D	E	E	F	E	E	D/F	E	E	E	E	F	D
D14S77	Y	Y	K	S		P	P	X	H		C	U	F	A
D14S78	7	7	1	5	7	7		6	7		3	7	2	6
D14S43	A	A	1	1	1	E	D	1	1		C	1	D	C
D14S273	6	6	3	5	5	4	4	4	6		6	6	5	3
D14S76	5	5	5	5	5	6	9	9			9	1	5	5
D14S61	E	E	G	F		1					D		L	F
D14S53	F	F	C	F	F	J	C	F	E		J	D	F	F
ETHNIC ORIGIN	Ashk	Ashk	Ital	Ital	Ital	Angl	Angl	Angl	Angl	Amer	FrCan	FrCan	Mex	G
MUTATION	C410Y	C410Y	M146L	M146L	ND	A246E	ND	ND	ND	H163R	H163R	ND	ND	L286V

TABLE 3

```
                                                                  Similarities
 No. Target File                      Key  Target   Overlap   Match    Percentages
  1  marmp.con/long [Frame 1]          1      1       467      465       99.57%

          1       10        20        30        40        50        60        70
Human N-  MTELPAPLSYFQNAQMSEDNHLSNTVRSQNDNRERQEHNDRRSLGHPEPLSNGRPQGNSRQVVEQDEEED
          ************************************************************************
Mouse N-  MTEIPAPLSYFQNAQMSEDSHSSSAIRSQNDSQERQQQHDRQRLDNPEPISNGRPQSNSRQVVEQDEEED
          1       10        20        30        40        50        60        70

         71       80        90       100       110       120       130       140
          EELTLKYGAKHVDMLFVPVTLCMVVVVATIKSVSFYTRKDGQLIYTPFTEDTETVGQRALHSILNAAIMI
          ************************************************************************
          EELTLKYGAKHVDMLFVPVTLCMVVVVATIKSVSFYTRKDGQLIYTPFTEDTETVGQRALHSILNAAIMI
         71       80        90       100       110       120       130       140

        141      150       160       170       180       190       200       210
          SVIVVMTILLVVLYKYRCYKVIHAWLIISSLLLLFFFSFIYLGIVFKTYNVAVDYITVALLINNLGVVGM
          ************************************************************************
          SVIVIMTILLVVLYKYRCYKVIHAWLIISSLLLLFFFSFIYLGEVFRTYNVXVDYVTVALLIWNWGVVGM
        141      150       160       170       180       190       200       210

        211      220       230       240       250       260       270       280
          ISIHWKGPLRLQQAYLIMISALMALVFIKYLPEWTAWLILAVISVYDLVAVLCPKGPLRMLVETAQERNE
          ************************************************************************
          ISIHWKGPLRLQQAYLIMISALMALVFIKYLPEWTAWLILAVISVYDLVAVLCPKGPLRMLVETAQERNE
        211      220       230       240       250       260       270       280
```

TABLE 3-continued

```
281      290       300       310       320       330       340       350
  TLFPALIYSSTMVWLVNMAEGDPEAQRRVSKNSKYNAESTERESQDTVAENDDGGFSEEMEAQRDSHLGP
  ************************** ** ************************************
  TLFPALIYSSTMVWLVNMAEGDPEAQRRVPKNPKYNTQRAERETQDSGSGNDDGGFSEEMEAQRDSHLGP
281      290       300       310       320       330       340       350

351      360       370       380       390       400       410       420
  HRSTPESRAAVQELSSSILAGEDPEERGVKGLGDFIFYSVLVGKASATASGDWNTTTIACFVAILIGLCL
  ************************************************************************
  HRSTPESRAAVQELSSSILAGEDPEERGVKGLGDFIFYSVLVGKASATASGDWNTTTIACFVAILIGLCL
351      360       370       380       390       400       410       420

421      430       440       450       460
  TLLLLAIFKKALPALPISITFGLVFYFATDYLVQPPMDQLAFHQFYI -C SEQ ID NO:2
  *********************************************
  XLLLLAIYKKGXPAXPISITFGFVFXFATDYLVQPFMDQLAFHQFYI -C SEQ ID NO:4
421      430       440       450       460
```

TABLE 4

HUMAN ARMP FUNCTION DOMAINS

Domains (Amino Acid Residue)			Functional Characteristic
82-100	AA		Hydrophobic
132-154	AA		Hydrophobic
164-183	AA		Hydrophobic
195-213	AA		Hydrophobic
221-238	AA		Hydrophobic
244-256	AA		Hydrophobic
281-299	AA		Hydrophobic
404-428	AA		Hydrophobic
431-449	AA		Hydrophobic
115-119	AA (YTPF)	SEQ ID NO: 161	Phosphorylation Site
353-356	AA (STPC)	SEQ ID NO: 162	Phosphorylation Site
300-385	AA		Acid Rich Domain
			Possible Metal Binding Domain

TABLE 4-continued

HUMAN ARMP FUNCTION DOMAINS

ANTIGENIC SITES INCLUDING AMINO ACID RESIDUES
27-44
46-48
50-60
66-67
107-111
120-121
125-126
155-160
185-189
214-223
220-230
240-245
267-269
273-282
300-370
400-420

TABLE 5

MUTATION	ENZYME (effect of mutation)	AMPLIFICATION 0440 #1	AMPLIFICATION 0440 #2	ALLELE-SPECIFIC 0440
M146LEU	BsphI (destroy)	910 (170-S182F) TCACAGAAGATACCG AGACT (SEQ ID NO:176)	911 (170-S182) R CCCAACCATAAGAAG AACAG (SEQ ID NO:177)	
MIS 164 Ary	Nla III (destroy)	927 (intronic) TCTGTACTTTTTAAG GGTTGTG (SEQ ID NO:178)	928 ACTTCAGAGTAATTC ATCANCA (SEQ ID NO:179)	
Ala 246	DLC I (create)	849* GACTCCAGCAGGCAT ATCT (SEQ ID NO:80)	892 TGAAATCACAGCCAA GATGAG (SEQ ID NO:130)	
Leu 286 Val.	Pvu II (create)	952 GATGAGACAAGTNCC NTGAA (SEQ ID NO:181)	951 CACCCATTTACAAGT TTAGC (SEQ ID NO:183)	

TABLE 5-continued

MUTATION	ENZYME (effect of mutation)	AMPLIFICATION 0440 #1	AMPLIFICATION 0440 #2	ALLELE-SPECIFIC 0440
		945 TTAGTGGCTGTTTNG TGTCC (SEQ ID NO:182)		
Cys 410 Tys	Allele specific ligo	893 GTGTGGCCAGGGTAG AGAACT (SEQ ID NO:128)	885 TGGAGACTGGAACAC AAC (SEQ ID NO:127)	CCATAGCCTGTTTCGTAGC (SEQ ID NO:131) 890 = WT CCATAGCCTATTTCGTAGC (SEQ ID NO:132) 891 = MUT

TABLE 6

POSITION OF EXONS AND INTRON-EXON BOUNDARIES OF THE ARMP GENE

cDNA/mRNA SEQUENCE		CORRESPONDING GENOMIC SEQUENCE	
ARMP (917 ver)	Transcript ID CC44 ver	Genomic sequence file ID & position of exon	Comments
1-113 bp	N/A	917-936.gen @ 731-834 bp	Alternate 5'UTR
N/A	1-422 bp	917-936.gen @ 1067-1475 bp	Alternate 5'UTR
114-195 bp	423-500 bp	932-943.gen @ 589-671 bp	
196-335 bp	501-632 bp	932-943.gen @ 759-899 bp	12 bp Variably spliced
337-586 bp	633-883 bp	901-912.gen @ 787-1037 bp	
587-730 bp	884-1026 bp	910-915.gen @ 1134-1278 bp	M146L mutation
731-795 bp	1027-1092 bp	925-913.gen @ 413-578 bp	B163R mutation
796-1017 bp	1093-1314 bp	849-892.gen @ 336-558 bp	A246E mutation
1018-1116 bp	1315-1413 bp	951-952.gen @ 312-412 bp	L286V mutation, variable spl
1117-1204 bp	1414-1501 bp	983-1011.gen @ 61-149 bp	
1205-1377 bp	1502-1674 bp	874-984.gen @ 452-625 bp	
1378-1497 bp	1674-1794 bp	885-1012.gen @ 431-550 bp	C410Y mutation
1493-2760 bp	1795-3060 bp	930-919.gen @ −10 bp-end	last AA, STOP, 3'UTR

TABLE 7

MUTATIONS AND POLYMORPHISMS IN THE ARMP GENE

Nucleotide # in ARMP.UPD	Amino acid # in ARMP.PRO	Comment
A->C_{684}	Met146Leu	Pathogenic, Unique to AD affected.
A->G_{736}	His163Arg	Pathogenic, Unique to AD affected.
C->A_{985}	Ala246Glu	Pathogenic, Unique to AD affected.
C->T_{1027}	Ala260Val	Pathogenic, Unique to AD affected.
C->T_{1102}	Ala285Val	Pathogenic, Unique to AD affected.

TABLE 7-continued

MUTATIONS AND POLYMORPHISMS IN THE ARMP GENE

Nucleotide # in ARMP.UPD	Amino acid # in ARMP.PRO	Comment
C->G_{1104}	Leu286Val	Pathogenic, Unique to AD affected.
C->G_{1422}	Leu392Val	Pathogenic, Unique to AD affected.
G->A_{1477}	Cys410Tyr	Pathogenic, Unique to AD affected.
G->T_{863}	Phe205Leu	Polymorphism in normals
C->A_{1700}	non-coding	3'UTR polymorphism
G->A_{2601}	non-coding	"
delC_{2620}	non-coding	"

SEQUENCE LISTING

<160> NUMBER OF SEQ ID NOS: 185

<210> SEQ ID NO 1
<211> LENGTH: 2791
<212> TYPE: DNA

-continued

<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(2791)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 1

tgggacaggc agctccgggg tccgcggttt cacatcggaa acaaaacagc ggctggtctg 60

gaaggaacct gagctacgag ccgcggcggc agcggggcgg cggggnaagc gtatacctaa 120

tctgggagcc tgcaagtgac aacagccttt gcggtcctta gacagcttgg cctggaggag 180

aacacatgaa agaaagaacc tcaagaggct ttgttttctg tgaaacagta tttctataca 240

gttgctccaa tgacagagtt acctgcaccg ttgtcctact tccagaatgc acagatgtct 300

gaggacaacc acctgagcaa tactgtacgt agccagaatg acaatagaga acggcaggag 360

cacaacgaca gacggagcct tggccaccct gagccattat ctaatggacg accccagggt 420

aactcccggc aggtggtgga gcaagatgag gaagaagatg aggagctgac attgaaatat 480

ggcgccaagc atgtgatcat gctctttgtc cctgtgactc tctgcatggt ggtggtcgtg 540

gctaccatta agtcagtcag cttttatacc cggaaggatg ggcagctaat ctatacccca 600

ttcacagaag ataccgagac tgtgggccag agagccctgc actcaattct gaatgctgcc 660

atcatgatca gtgtcattgt tgtcatgact atcctcctgg tggttctgta taaatacagg 720

tgctataagg tcatccatgc ctggcttatt atatcatctc tattgttgct gttctttttt 780

tcattcattt acttgggggga agtgtttaaa acctataacg ttgctgtgga ctacattact 840

gttgcactcc tgatctggaa tttgggtgtg gtgggaatga tttccattca ctggaaaggt 900

ccacttcgac tccagcaggc atatctcatt atgattagtg ccctcatggc cctggtgttt 960

atcaagtacc tccctgaatg gactgcgtgg ctcatcttgg ctgtgatttc agtatatgat 1020

ttagtggctg ttttgtgtcc gaaaggtcca cttcgtatgc tggttgaaac agctcaggag 1080

agaaatgaaa cgctttttcc agctctcatt tactcctcaa caatggtgtg gttggtgaat 1140

atggcagaag gagacccgga agctcaaagg agagtatcca aaaattccaa gtataatgca 1200

gaaagcacag aaagggagtc acaagacact gttgcagaga atgatgatgg cgggttcagt 1260

gaggaatggg aagcccagag ggacagtcat ctagggcctc atcgctctac acctgagtca 1320

cgagctgctg tccaggaact ttccagcagt atcctcgctg gtgaagaccc agaggaaagg 1380

ggagtaaaac ttggattggg agatttcatt ttctacagtg ttctggttgg taaagcctca 1440

gcaacagcca gtggagactg gaacacaacc atagcctgtt tcgtagccat attaattggt 1500

ttgtgcctta cattattact ccttgccatt ttcaagaaag cattgccagc tcttccaatc 1560

tccatcacct ttgggcttgt tttctacttt gccacagatt atcttgtaca gccttttatg 1620

gaccaattag cattccatca attttatatc tagcatattt gcggttagaa tcccatggat 1680

gtttcttctt tgactataac caaatctggg gaggacaaag gtgattttcc tgtgtccaca 1740

tctaacaaag tcaagattcc cggctggact tttgcagctt ccttccaagt cttcctgacc 1800

accttgcact attggacttt ggaaggaggt gcctatagaa aacgattttg aacatacttc 1860

atcgcagtgg actgtgtcct cggtgcagaa actaccagat ttgagggacg aggtcaagga 1920

gatatgatag gcccggaagt tgctgtgccc catcagcagc ttgacgcgtg gtcacaggac 1980

gatttcactg acactgcgaa ctctcaggac taccggttac caagaggtta ggtgaagtgg 2040

tttaaaccaa acggaactct tcatcttaaa ctacacgttg aaaatcaacc caataattct 2100

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gtattaactg aattctgaac ttttcaggag gtactgtgag gaagagcagg caccagcagc 2160

agaatgggga atggagaggt gggcaggggt tccagcttcc ctttgatttt ttgctgcaga 2220

ctcatccttt ttaaatgaga cttgttttcc cctctctttg agtcaagtca aatatgtaga 2280

tgcctttggc aattcttctt ctcaagcact gacactcatt accgtctgtg attgccattt 2340

cttcccaagg ccagtctgaa cctgaggttg ctttatccta aaagttttaa cctcaggttc 2400

caaattcagt aaattttgga aacagtacag ctatttctca tcaattctct atcatgttga 2460

agtcaaattt ggattttcca ccaaattctg aatttgtaga catacttgta cgctcacttg 2520

ccccagatgc ctcctctgtc ctcattcttc tctcccacac aagcagtctt tttctacagc 2580

cagtaaggca gctctgtcgt ggtagcagat ggtcccactt attctagggt cttactcttt 2640

gtatgatgaa aagaatgtgt tatgaatcgg tgctgtcagc cctgctgtca gaccttcttc 2700

cacagcaaat gagatgtatg cccaaagcgg tagaattaaa gaagagtaaa atggctgttg 2760

aagcaaaaaa aaaaaaaaaa aaaaaaaaaa a 2791

<210> SEQ ID NO 2
<211> LENGTH: 467
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 2

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1 5 10 15

Ser Glu Asp Asn His Leu Ser Asn Thr Val Arg Ser Gln Asn Asp Asn
20 25 30

Arg Glu Arg Gln Glu His Asn Asp Arg Arg Ser Leu Gly His Pro Glu
35 40 45

Pro Leu Ser Asn Gly Arg Pro Gln Gly Asn Ser Arg Gln Val Val Glu
50 55 60

Gln Asp Glu Glu Glu Asp Glu Glu Leu Thr Leu Lys Tyr Gly Ala Lys
65 70 75 80

His Val Ile Met Leu Phe Val Pro Val Thr Leu Cys Met Val Val Val
85 90 95

Val Ala Thr Ile Lys Ser Val Ser Phe Tyr Thr Arg Lys Asp Gly Gln
100 105 110

Leu Ile Tyr Thr Pro Phe Thr Glu Asp Thr Glu Thr Val Gly Gln Arg
115 120 125

Ala Leu His Ser Ile Leu Asn Ala Ala Ile Met Ile Ser Val Ile Val
130 135 140

Val Met Thr Ile Leu Leu Val Val Leu Tyr Lys Tyr Arg Cys Tyr Lys
145 150 155 160

Val Ile His Ala Trp Leu Ile Ile Ser Ser Leu Leu Leu Leu Phe Phe
165 170 175

Phe Ser Phe Ile Tyr Leu Gly Glu Val Phe Lys Thr Tyr Asn Val Ala
180 185 190

Val Asp Tyr Ile Thr Val Ala Leu Leu Ile Trp Asn Leu Gly Val Val
195 200 205

Gly Met Ile Ser Ile His Trp Lys Gly Pro Leu Arg Leu Gln Gln Ala
210 215 220

Tyr Leu Ile Met Ile Ser Ala Leu Met Ala Leu Val Phe Ile Lys Tyr
225 230 235 240

Leu Pro Glu Trp Thr Ala Trp Leu Ile Leu Ala Val Ile Ser Val Tyr
245 250 255

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Asp Leu Val Ala Val Leu Cys Pro Lys Gly Pro Leu Arg Met Leu Val
            260                 265                 270

Glu Thr Ala Gln Glu Arg Asn Glu Thr Leu Phe Pro Ala Leu Ile Tyr
        275                 280                 285

Ser Ser Thr Met Val Trp Leu Val Asn Met Ala Glu Gly Asp Pro Glu
    290                 295                 300

Ala Gln Arg Arg Val Ser Lys Asn Ser Lys Tyr Asn Ala Glu Ser Thr
305                 310                 315                 320

Glu Arg Glu Ser Gln Asp Thr Val Ala Glu Asn Asp Asp Gly Gly Phe
                325                 330                 335

Ser Glu Glu Trp Glu Ala Gln Arg Asp Ser His Leu Gly Pro His Arg
            340                 345                 350

Ser Thr Pro Glu Ser Arg Ala Ala Val Gln Glu Leu Ser Ser Ser Ile
        355                 360                 365

Leu Ala Gly Glu Asp Pro Glu Glu Arg Gly Val Lys Leu Gly Leu Gly
    370                 375                 380

Asp Phe Ile Phe Tyr Ser Val Leu Val Gly Lys Ala Ser Ala Thr Ala
385                 390                 395                 400

Ser Gly Asp Trp Asn Thr Thr Ile Ala Cys Phe Val Ala Ile Leu Ile
                405                 410                 415

Gly Leu Cys Leu Thr Leu Leu Leu Leu Ala Ile Phe Lys Lys Ala Leu
            420                 425                 430

Pro Ala Leu Pro Ile Ser Ile Thr Phe Gly Leu Val Phe Tyr Phe Ala
        435                 440                 445

Thr Asp Tyr Leu Val Gln Pro Phe Met Asp Gln Leu Ala Phe His Gln
    450                 455                 460

Phe Tyr Ile
465


<210> SEQ ID NO 3
<211> LENGTH: 1929
<212> TYPE: DNA
<213> ORGANISM: Mus musculus
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1929)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u,
      unknown or other

<400> SEQUENCE: 3

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agagaaggaa ccaacacaag acagcagccc ttcgaggtct ttaggcagct tggaggagaa    120

cacatgagag aaagaatccc aagaggtttt gttttctttg agaaggtatt tctgtccagc    180

tgctccaatg acagagatac ctgcaccttt gtcctacttc cagaatgccc agatgtctga    240

ggacagccac tccagcagcg ccatccggag ccagaatgac agccaagaac ggcagcagca    300

gcatgacagg cagagacttg acaaccctga gccaatatct aatgggcggc cccagagtaa    360

ctcaagacag gtggtggaac aagatgagga ggaagacgaa gagctgacat tgaaatatgg    420

agccaagcat gtcatcatgc tctttgtccc cgtgaccctc tgcatggtcg tcgtcgtggc    480

caccatcaaa tcagtcagct tctatacccg gaaggacggt cagctaatct acaccccatt    540

cacagaagac actgagactg taggccaaag agccctgcac tcgatcctga atgcggccat    600

catgatcagt gtcattgtca ttatgaccat cctcctggtg gtcctgtata aatacaggtg    660

ctacaaggtc atccacgcct ggcttattat ttcatctctg ttgttgctgt tctttttttc    720
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gttcatttac ttaggggaag tatttaagac ctacaatgtc kccgtggact acgttacagt 780

agcactccta atctggaatt ggggtgtggt cgggatgatt gccatccact ggaaaggccc 840

ccttcgactg cagcaggcgt atctcattat gatcagtgcc ctcatggccc tggtatttat 900

caagtacctc cccgaatgga ccgcatggct catcttggct gtgatttcag tatatgattt 960

ggtggctgtt ttatgtccca aaggcccact tcgtatgctg gttgaaacag ctcaggaaag 1020

aaatgagact ctctttccag ctcttatcta ttcctcaaca atggtgtggt tggtgaatat 1080

ggctgaagga gacccagaag cccaaaggag ggtacccaag aaccccaagt ataacacaca 1140

aagagcggag agagagacac aggacagtgg ttctgggaac gatgatggtg gcttcagtga 1200

ggagtgggag gcccaaagag acagtcacct ggggcctcat cgctccactc ccgagtcaag 1260

agctgctgtc caggaacttt ctgggagcat tctaacgagt gaagacccgg aggaaagagg 1320

agtaaaactt ggactgggag atttcatttt ctacagtgtt ctggttggta aggcctcagc 1380

aaccgccagt ggagactgga acacaaccat agcctgcttk gtagccatac tgatcggcct 1440

gtgccttana ttactcctgc tcgccattta caagaaaggg tngccagccc nccccatctc 1500

catcaccttc gggttcgtgt tctncttcgc cacggattac cttgtgcagc ccttcatgga 1560

ccaacttgca ttccatcagt tttatatcta gcctttctgc agttagaaca tggatgtttc 1620

ttctttgatt atcaaaaaca caaaaacaga gagcaagccc gaggaggaga ctggtgactt 1680

tcctgtgtcc tcagctaaca aaggcaggac tccagctgga cttctgcagc ttccttccga 1740

gtctccctag ccacccgcac tactggactg tggaaggaag cgtctacaga ggaacggttt 1800

ccaacatcca tcgctgcagc agacggtgtc cctcagtgac ttgagagaca aggacaagga 1860

aatgtgctgg gccaaggagc tgccgtgctc tgctagcttt ggmccgtggg catggagatt 1920

tacccgcac 1929

<210> SEQ ID NO 4
<211> LENGTH: 467
<212> TYPE: PRT
<213> ORGANISM: Mus musculus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(467)
<223> OTHER INFORMATION: where X is unknown or other

<400> SEQUENCE: 4

Met Thr Glu Ile Pro Ala Pro Leu Ser Tyr Phe Gln Asn Ala Gln Met
1 5 10 15

Ser Glu Asp Ser His Ser Ser Ser Ala Ile Arg Ser Gln Asn Asp Ser
20 25 30

Gln Glu Arg Gln Gln Gln His Asp Arg Gln Arg Leu Asp Asn Pro Glu
35 40 45

Pro Ile Ser Asn Gly Arg Pro Gln Ser Asn Ser Arg Gln Val Val Glu
50 55 60

Gln Asp Glu Glu Glu Asp Glu Glu Leu Thr Leu Lys Tyr Gly Ala Lys
65 70 75 80

His Val Ile Met Leu Phe Val Pro Val Thr Leu Cys Met Val Val Val
85 90 95

Val Ala Thr Ile Lys Ser Val Ser Phe Tyr Thr Arg Lys Asp Gly Gln
100 105 110

Leu Ile Tyr Thr Pro Phe Thr Glu Asp Thr Glu Thr Val Gly Gln Arg
115 120 125

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Ala Leu His Ser Ile Leu Asn Ala Ala Ile Met Ile Ser Val Ile Val
    130                 135                 140

Ile Met Thr Ile Leu Leu Val Val Leu Tyr Lys Tyr Arg Cys Tyr Lys
145                 150                 155                 160

Val Ile His Ala Trp Leu Ile Ile Ser Ser Leu Leu Leu Leu Phe Phe
                165                 170                 175

Phe Ser Phe Ile Tyr Leu Gly Glu Val Phe Lys Thr Tyr Asn Val Xaa
            180                 185                 190

Val Asp Tyr Val Thr Val Ala Leu Leu Ile Trp Asn Trp Gly Val Val
        195                 200                 205

Gly Met Ile Ala Ile His Trp Lys Gly Pro Leu Arg Leu Gln Gln Ala
    210                 215                 220

Tyr Leu Ile Met Ile Ser Ala Leu Met Ala Leu Val Phe Ile Lys Tyr
225                 230                 235                 240

Leu Pro Glu Trp Thr Ala Trp Leu Ile Leu Ala Val Ile Ser Val Tyr
                245                 250                 255

Asp Leu Val Ala Val Leu Cys Pro Lys Gly Pro Leu Arg Met Leu Val
            260                 265                 270

Glu Thr Ala Gln Glu Arg Asn Glu Thr Leu Phe Pro Ala Leu Ile Tyr
        275                 280                 285

Ser Ser Thr Met Val Trp Leu Val Asn Met Ala Glu Gly Asp Pro Glu
    290                 295                 300

Ala Gln Arg Arg Val Pro Lys Asn Pro Lys Tyr Asn Thr Gln Arg Ala
305                 310                 315                 320

Glu Arg Glu Thr Gln Asp Ser Gly Ser Gly Asn Asp Asp Gly Gly Phe
                325                 330                 335

Ser Glu Glu Trp Glu Ala Gln Arg Asp Ser His Leu Gly Pro His Arg
            340                 345                 350

Ser Thr Pro Glu Ser Arg Ala Ala Val Gln Glu Leu Ser Gly Ser Ile
        355                 360                 365

Leu Thr Ser Glu Asp Pro Glu Glu Arg Gly Val Lys Leu Gly Leu Gly
    370                 375                 380

Asp Phe Ile Phe Tyr Ser Val Leu Val Gly Lys Ala Ser Ala Thr Ala
385                 390                 395                 400

Ser Gly Asp Trp Asn Thr Thr Ile Ala Cys Xaa Val Ala Ile Leu Ile
                405                 410                 415

Gly Leu Cys Leu Xaa Leu Leu Leu Leu Ala Ile Tyr Lys Lys Gly Xaa
            420                 425                 430

Pro Ala Xaa Pro Ile Ser Ile Thr Phe Gly Phe Val Phe Xaa Phe Ala
        435                 440                 445

Thr Asp Tyr Leu Val Gln Pro Phe Met Asp Gln Leu Ala Phe His Gln
    450                 455                 460

Phe Tyr Ile
465
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<210> SEQ ID NO 5
<211> LENGTH: 3087
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(3087)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 5

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tgggtctgct tgagcaactg gtgaaactcc gcgcctcacg ccccgggtgt gtccttgtcc    180
aggggcgacg agcattctgg gcgaagtccg cacscctctt gttcgaggcg gaagacgggg    240
tctgatsctt tctccttggt cgggmctgtc tcgaggcatg catgtccagt gactcttgtg    300
tttgctgctg cttccctctc agattcttct caccgttgtg gtcagctctg ctttaggcan    360
tattaatcca tagtggaggc tgggatgggt gagagaattg aggtgacttt tccataattc    420
agacctaatc tgggagcctg caagtgacaa cagcctttgc ggtccttaga cagcttggcc    480
tggaggagaa cacatgaaag aaagaacctc aagaggcttt gttttctgtg aaacagtatt    540
tctatacagt tgctccaatg acagagttac ctgcaccgtt gtcctacttc cagaatgcac    600
agatgtctga ggacaaccac ctgagcaata ctaatgacaa tagagaacgg caggagcaca    660
acgacagacg gagccttggc caccctgagc cattatctaa tggacgaccc cagggtaact    720
cccggcaggt ggtggagcaa gatgaggaag aagatgagga gctgacattg aaatatggcg    780
ccaagcatgt gatcatgctc tttgtccctg tgactctctg catggtggtg gtcgtggcta    840
ccattaagtc agtcagcttt tatacccgga aggatgggca gctaatctat accccattca    900
cagaagatac cgagactgtg ggccagagag ccctgcactc aattctgaat gctgccatca    960
tgatcagtgt cattgttgtc atgactatcc tcctggtggt tctgtataaa tacaggtgct   1020
ataaggtcat ccatgcctgg cttattatat catctctatt gttgctgttc tttttttcat   1080
tcatttactt gggggaagtg tttaaaacct ataacgttgc tgtggactac attactgttg   1140
cactcctgat ctggaatttg ggtgtggtgg gaatgatttc cattcactgg aaaggtccac   1200
ttcgactcca gcaggcatat ctcattatga ttagtgccct catggccctg gtgtttatca   1260
agtacctccc tgaatggact gcgtggctca tcttggctgt gatttcagta tatgatttag   1320
tggctgtttt gtgtccgaaa ggtccacttc gtatgctggt tgaaacagct caggagagaa   1380
atgaaacgct ttttccagct ctcatttact cctcaacaat ggtgtggttg gtgaatatgg   1440
cagaaggaga cccggaagct caaaggagag tatccaaaaa ttccaagtat aatgcagaaa   1500
gcacagaaag ggagtcacaa gacactgttg cagagaatga tgatggcggg ttcagtgagg   1560
aatgggaagc ccagagggac agtcatctag ggcctcatcg ctctacacct gagtcacgag   1620
ctgctgtcca ggaactttcc agcagtatcc tcgctggtga agacccagag gaaaggggag   1680
taaaacttgg attgggagat ttcattttct acagtgttct ggttggtaaa gcctcagcaa   1740
cagccagtgg agactggaac acaaccatag cctgtttcgt agccatatta attggtttgt   1800
gccttacatt attactcctt gccattttca agaaagcatt gccagctctt ccaatctcca   1860
tcacctttgg gcttgttttc tactttgcca cagattatct tgtacagcct tttatggacc   1920
aattagcatt ccatcaattt tatatctagc atatttgcgg ttagaatccc atggatgttt   1980
cttctttgac tataaccaaa tctggggagg acaaaggtga ttttcctgtg tccacatcta   2040
acaaagtcaa gattcccggc tggacttttg cagcttcctt ccaagtcttc ctgaccacct   2100
tgcactattg gactttggaa ggaggtgcct atagaaaacg attttgaaca tacttcatcg   2160
cagtggactg tgtcctcggt gcagaaacta ccagatttga gggacgaggt caaggagata   2220
tgataggccc ggaagttgct gtgccccatc agcagcttga cgcgtggtca caggacgatt   2280
tcactgacac tgcgaactct caggactacc ggttaccaag aggttaggtg aagtggttta   2340
aaccaaacgg aactcttcat cttaaactac acgttgaaaa tcaacccaat aattctgtat   2400
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taactgaatt ctgaactttt caggaggtac tgtgaggaag agcaggcacc agcagcagaa 2460

tggggaatgg agaggtgggc aggggttcca gcttcccttt gatttttgc tgcagactca 2520

tccttttaa atgagacttg ttttcccctc tctttgagtc aagtcaaata tgtagatgcc 2580

tttggcaatt cttcttctca agcactgaca ctcattaccg tctgtgattg ccatttcttc 2640

ccaaggccag tctgaacctg aggttgcttt atcctaaaag ttttaacctc aggttccaaa 2700

ttcagtaaat tttggaaaca gtacagctat ttctcatcaa ttctctatca tgttgaagtc 2760

aaatttggat tttccaccaa attctgaatt tgtagacata cttgtacgct cacttgcccc 2820

agatgcctcc tctgtcctca ttcttctctc ccacacaagc agtctttttc tacagccagt 2880

aaggcagctc tgtcgtggta gcagatggtc ccacttattc tagggtctta ctctttgtat 2940

gatgaaaaga atgtgttatg aatcggtgct gtcagccctg ctgtcagacc ttcttccaca 3000

gcaaatgaga tgtatgccca aagcggtaga attaaagaag agtaaaatgg ctgttgaagc 3060

aaaaaaaaaa aaaaaaaaaa aaaaaaa 3087

<210> SEQ ID NO 6
<211> LENGTH: 945
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(945)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 6

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aaagactnca gttgagccgt gattgcaccc actttactcc aagcctgggc aaccaaaatg 120

agacactggc tccaaacaca aaaacaaaaa caaaaaaaga gtaaattaat ttanagggaa 180

gnattaaata aataatagca cagttgatat aggttatggt aaaattataa aggtgggana 240

ttaatatcta atgtttggga gccatcacat tattctaaat aatgttttgg tggaaattat 300

tgtacatctt ttaaaatctg tgtaattttt tttcagggaa gtgtttaaaa cctataacgt 360

tgctgtggac tacattactg ttncactcct gatctggaat tttggtgtgg tgggaatgat 420

ttccattcac tggaaaggtc cacttcgact ccagcaggca tatctcatta tgattagtgc 480

cctcatgncc ctgktgttta tcaagtacct ccctgaatgg actgngtggc tcatcttggc 540

tgtgatttca gtatatggta aaacccaaga ctgataattt gtttgtcaca ggaatgcccc 600

actggagtgt tttctttcct catctcttta tcttgattta gagaaaatgg taacgtgtac 660

atcccataac tcttcagtaa atcattaatt agctatagta acttttтcat ttgaagattt 720

cggctgggca tggtagctca tgcctgtaat cttagcactt tgggaggctg aggcgggcag 780

atcacctaag cccagagttc aagaccagcc tgggcaacat ggcaaaacct cgtatctaca 840

gaaaatacaa aaattagccg ggcatggtgg tgcacacctg tagttccagc tacttaggag 900

gctgaggtgg gaggatcgat tgatcccagg aggtcaagnc tgcag 945

<210> SEQ ID NO 7
<211> LENGTH: 450
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(450)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u,

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unknown or other

<400> SEQUENCE: 7

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aatagtgctt ttttttttt ttttttttt ttttttttt tttggggana gagtctcgct 180

ctgtcgccag gttggagtgc aatggtgcga tcttggctca ctgaaagctc caccncccgg 240

gttcaagtga ttctcctgcc tcagccnccc aagtagntgg gactacaggg gtgcgccacc 300

acgcctggga taattttggg nttttagta gagatggcgt ttcaccanct tggngcaggc 360

tggtcttgga actcctgana tcatgatctg cctgccttag cctccccaaa gtgctgggat 420

tncaggggtg agccactgtt cctgggcctc 450

<210> SEQ ID NO 8
<211> LENGTH: 516
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(516)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 8

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tgctcccgca caggatagag aatgcccccg cacagcatag agaagccccc gcacagcata 120

gagaatgccc ccncacagca tagagaagcc cccgcacagc atagagaatg ctcttcacct 180

ctgggttttt aaccagccaa actaaaatca cagaggscma cacatcattt aagatagaaa 240

tttctgtatc ttttaattty tttcmaagta gttttactta ttttcagatt ctatttcttt 300

actagaatta agggataaaa taacaatgtg tgcataatga accctatgaa acmaacmmaa 360

gctaggtttt tttcatagst cttcttccag attgaatgaa cgtctgttct aaaatttaac 420

cccccaggga aatattcagt taactatgtt aaaaacccag acttgtgatt gagttttgcc 480

tgaaaatgct ttcataatta tgtgtgaatg tgtgtc 516

<210> SEQ ID NO 9
<211> LENGTH: 1726
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1726)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 9

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aactgtcatg gtgttggcgg ggagtgtctt ttagcatgct aatgtattat aattagcgta 120

tagtgagcag tgaggataac cagaggtcac tctcctcacc atcttggttt tggtgggttt 180

tggccagctt ctttattgca accagtttta tcagcaagat ctttatgagc tgtatcttgt 240

gctgacttcc tatctcatcc cgnaactaag agtacctaac ctcctgcaaa ttgmagncca 300

gnaggtcttg gncttatttn acccagcccc tattcaarat agagtngytc ttggnccaaa 360

cgccyctgac acaaggattt taaagtctta ttaattaagg taagatagkt ccttgsatat 420

gtggtctgaa atcacagaaa gctgaatttg gaaaaaggtg cttggasctg cagccagtaa 480

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acaagttttc atgcaggtgt cagtatttaa ggtacatctc aaaggataag tacaattgtg 540

tatgttggga tgaacagaga gaatggagca anccaagacc caggtaaaag agaggacctg 600

aatgccttca gtgaacaatg atagataatc tagactttta aactgcatac ttcctgtaca 660

ttgtttttttc ttgcttcagg tttttagaac tcatagtgac gggtctgttg ttaatcccag 720

gtctaaccgt taccttgatt ctgctgagaa tctgatttac tgaaaatgtt tttcttgtgc 780

ttatagaatg acaatagaga acggcaggag cacaacgaca gacggagcct tggccaccct 840

ganccattat ctaatggacg acccagggta actcccggca ggtggtggan caagatgagg 900

aagaagatga gganctgaca ttgaaatatg ncgscaagca tgtgatcatg ctctttgkcc 960

ctgtgactct ctgcatggtg gtggtcgtgg ntaccattaa gtcagtcagc ttttataccc 1020

ggaaggatgg gcagctgtac gtatgagttt kgttttatta ttctcaaasc cagtgtggct 1080

tttctttaca gcatgtcatc atcaccttga aggcctctnc attgaagggg catgacttag 1140

ctggagagcc catcctctgt gatggtcagg agcagttgag agancgaggg gttattactt 1200

catgttttaa gtggagaaaa ggaacactgc agaagtatgt ttcctgtatg gtattactgg 1260

atagggctga agttatgctg aattgaacac ataaattctt ttccacctca gggncattgg 1320

gcgcccattg ntcttctgcc tagaatattc tttcctttnc tnacttkggn ggattaaatt 1380

cctgtcatcc ccctcctctt ggtgttatat ataaagtntt ggtgccgcaa aagaagtagc 1440

actcgaatat aaaattttcc ttttaattct cagcaaggna agttacttct atatagaagg 1500

gtgcacccnt acagatggaa caatggcaag cgcacatttg ggacaaggga ggggaaaggg 1560

ttcttatccc tgacacacgt ggtcccngct gntgtgtnct ncccccactg antagggtta 1620

gactggacag gcttaaacta attccaattg gntaatttaa agagaatnat ggggtgaatg 1680

ctttgggagg agtcaaggaa gagnaggtag naggtaactt gaatga 1726

<210> SEQ ID NO 10
<211> LENGTH: 1883
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1883)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 10

cncgtataaa agaccaacat tgccancnac aaccacaggc aagatcttct cctaccttcc 60

cccnnggtgt aataccaagt attcnccaat ttgtgataaa ctttcattgg aaagtgacca 120

ccctccttgg ttaatacatt gtctgtgcct gctttcacac tacagtagca cagttgagtg 180

tttgccctgg agaccatatg acccatagag cttaaaatat tcagtctggc tttttacaga 240

gatgtttctg actttgttaa tagaaaatca acccaactgg tttaaataat gcacatactt 300

tctctctcat agagtagtgc agaggtagnc agtccagatt agtasggtgg cttcacgttc 360

atccaaggac tcaatctcct tctttcttct ttagcttcta acctctagct tacttcaggg 420

tccaggctgg agccctascc ttcatttctg acagtaggaa ggagtagggg agaaaagaac 480

ataggacatg tcagcagaat tctctcctta gaagttccat acacaacaca tctccctaga 540

agtcattgcc cttacttgtt ctcatagcca tcctaaatat aagggagtca gaagtaaagt 600

ctkkntggct gggaatattg gcacctggaa taaaaatgtt tttctgtgaa tgagaaacaa 660

ggggaagatg gatatgtgac attatcttaa gacaactcca gttgcaatta ctctgcagat 720

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gagaggcact aattataagc catattacct ttcttctgac aaccacttgt cagcccncgt 780

ggtttctgtg gcagaatctg gttcyatamc aagttcctaa taanctgtas ccnaaaaaat 840

ttgatgaggt attataatta tttcaatata aagcacccac tagatggagc cagtgtctgc 900

ttcacatgtt aagtccttct ttccatatgt tagacatttt ctttgaagca attttagagt 960

gtagctgttt ttctcaggtt aaaaattctt agctaggatt ggtgagttgg ggaaaagtga 1020

cttataagat ncgaattgaa ttaagaaaaa gaaaattctg tgttggaggt ggtaatgtgg 1080

ktggtgatct ycattaacac tganctaggg ctttkgkgtt tgktttattg tagaatctat 1140

accccattca nagaagatac cgagactgtg ggccagagag ccctgcactc aattctgaat 1200

gctgccatca tgatcagngt cattgtwgtc atgactannc tcctggtggt tcwgtataaa 1260

tacaggtgct ataaggtgag catgagacac agatctttgn tttccaccct gttcttctta 1320

tggttgggta ttcttgtcac agtaacttaa ctgatctagg aaagaaaaaa tgttttgtct 1380

tctagagata agttaatttt tagttttctt cctcctcact gtggaacatt caaaaaatac 1440

aaaaaggaag ccaggtgcat gtgtaatgcc aggctcagag gctgaggcag gaggatcgct 1500

tgggcccagg agttcacaag cagcttgggc aacgtagcaa gaccctgcct ctattaaaga 1560

aaacaaaaaa caaatattgg aagtatttta tatgcatgga atctatatgt catgaaaaaa 1620

ttagtgtaaa atatatatat tatgattagn tatcaagatt tagtgataat ttatgttatt 1680

ttgggatttc aatgcctttt taggccattg tctcaamaaa taaaagcaga aaacaaaaaa 1740

agttgtaact gaaaaataaa catttccata taatagcaca atctaagtgg gtttttgntt 1800

gtttgtttgn ttgttgaagc agggccttgc cctnycaccc aggntggagt gaagtgcagt 1860

ggcacgattt tggctcactg cag 1883

<210> SEQ ID NO 11
<211> LENGTH: 823
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(823)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 11

caggagtgga ctaggtaaat gnaagntgtt ttaaagagag atgnggncng ggacatagtg 60

gtacacanct gtaatgctca ncactkatgg ggagtactga aggnggnsgg atcacttgng 120

ggtcnggaat ntgagancag cctgggcaan atggcgaaac cctgtctcta ctaaaaatag 180

ccanaawnwa gcctagcgtg gtggcgcrca cgcgtggttc cacctactca ggaggcntaa 240

gcacgagnan tncttgaacc caggaggcag aggntgtggt garctgagat cgtgccactg 300

cactccagtc tgggcgacma agtgagaccc tgtctccnnn aagaaaaaaa aaatctgtac 360

tttttaaggg ttgtgggacc tgttaattat attgaaatgc ttctyttcta ggtcatccat 420

gcctggctta ttatatcatc tctattgttg ctgctctttt ttacattcat ttacttgggg 480

taagttgtga aatttggggt ctgtctttca gaattaacta cctnngtgct gtgtagctat 540

catttaaagc catgtacttt gntgatgaat tactctgaag ttttaattgt ntccacatat 600

aggtcatact tggtatataa aagactagnc agtattacta attgagacat tcttctgtng 660

ctcctngctt ataataagta gaactgaaag naacttaaga ctacagttaa ttctaagcct 720

ttggggaagg attatatagc cttctagtag gaagtcttgt gcnatcagaa tgtttntaaa 780

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gaaagggtnt caaggaatng tataaanacc aaaaataatt gat 823

<210> SEQ ID NO 12
<211> LENGTH: 736
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 12

gtctttccca tcttctccac agagtttgtg ccttacatta ttactccttg ccattttcaa 60

gaaagcattg tcagctcttc caatctccat cacctttggg cttgttttct actttgccac 120

agattatctt gtacagcctt ttatggacca attagcattc catcaatttt atatctagca 180

tatttgcggt tagaatccca tggatgtttc ttctttgact ataacaaaat ctggggagga 240

caaaggtgat ttcctgtgtc cacatctaac aaatcaagat ccccggctgg acttttggag 300

gttccttcca agtcttcctg accaccttgc actattggac tttggaagga ggtgcctata 360

gaaaacgatt ttgaacatac ttcatcgcag tggactgtgt cctcggtgca gaaactacca 420

gatttgaggg acgaggtcaa ggagatatga taggcccgga agttgctgtg ccccatcagc 480

agcttgacgc gtggtcacag gacgattttc actgacactg cgaactctca ggactaccgt 540

taccaagagg ttaggtgaag tggtttaaac caaacggaac tcttcatctt aaactacacg 600

ttgaaaatca acccaataat tctgtattaa ctgaattctg aacttttcag gaggtactgt 660

gaggaagagc aggcaccacc agcagaatgg ggaatggaga ggtgggcagg ggttccagct 720

tccctttgat tttttg 736

<210> SEQ ID NO 13
<211> LENGTH: 893
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(893)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 13

ggatccgccc gccttggcct cccaaagtgc tgggattaca ggcatgagcc accgctcctg 60

gctgagtctg cgatttcttg ccagctctac ccagttgtgt catcttaagc aagtcactga 120

acttctctgg attcccttct cctnnwgtaa aataagnatg ttatctgncc nncctgcctt 180

gggcattgtg ataaggataa gatgacatta tagaatntng caaaattaaa agcgctagac 240

aaatgatttt atgaaaatat aaagattagn ttgagtttgg gccagcatag aaaaaggaat 300

gttgagaaca ttccnttaag gattactcaa gcyccccttt tgstgknwaa tcaganngtc 360

atnnamntat cntntgtggg ytgaaaatgt ttggttgtct caggcggttc ctacttattg 420

ctaaagagtc ctaccttgag cttatagtaa atttgtcagt tagttgaaag tcgtgacaaa 480

ttaatacatt cctggtttac aaattggtct tataagtatt tgattggtnt aaatgnattt 540

actaggattt aactaacaat ggatgacctg gtgaaatcct atttcagacc taatctggga 600

gcctgcaagt gacaacagcc tttgcggtcc ttagacagct tggcctggag gagaacacat 660

gaaagaaagg tttgtttctg cttaatgtaa tctatggaag tgtttttttat aacagtataa 720

ttgtagtgca caaagttctg tttttctttc ccttttcaga acctcaagag gctttgtttt 780

ctgtgaaaca gtatttctat acagtntgct ccaantgnac agagttacct gcacnncgtt 840

gtccntactt ccagaatgca cagatgtctg aggacaacca cctgagcaat act 893

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<210> SEQ ID NO 14
<211> LENGTH: 475
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(475)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 14

tcagaaaata ctttngggca catgagaatc acatgagaac aagctgatgc ataattcctc 60

ctgtgatgga atgtaatagt aatttaacag tgtccttttct ttttaactgc ctcaaggata 120

cagcaaaata aaacaaaagc aatatgaagg ctgagaatag gtatcagatt atcataaaaa 180

gtatagatca aaaggaatct ggtkctnagg ttggcgcagc agcctctaga agcgacnagg 240

gagactttta gaactaccat tctcctctat aagtggatcc nangcccagg raaacttgat 300

attgagnaca atggccttac tgaaataacc tgtgatccac tcggnctcat catctccacc 360

accaccataa atttgatgag tncctataat attccancca gnggaaatac ctggraggtt 420

actgaaaggc nacnatcaga cnaaaataaa gnataccgta ggtaaattct acagt 475

<210> SEQ ID NO 15
<211> LENGTH: 180
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(180)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 15

gttctcnaga tctcttcaaa attcattntg cgctatagga gctgggatta ccgcgggtgc 60

tggaaccaga cttgcnctcc aatggatcct ccanacngga ngggggggtgg actcacacca 120

tttacagggg gctcgtaaag aatcctgttt tgantattnt nccgtcaatt accncccaa 180

<210> SEQ ID NO 16
<211> LENGTH: 457
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(457)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 16

aatgtaacma cmaaaccyca aactcctgna agaanatggt tacttatnga tnccatttnc 60

tttttncact ctcagacata aatataaacm mantttctac tgtggraaaa catctncagg 120

ggncntttan ccatgatctc tagnacnang ggctngtggn tngttttaat gtctctaagc 180

nactngacta gtttctcttn cactgagnaa actgcnacaa gtnnttnctn ctgnatctgn 240

actgnaatgc taagttncaa gtnccaatga gctngtgant tanyctttat ttnamcnaaa 300

gtnnttaatc anccncagtg ttactttgna aagctnctcc ctggacaggc ggcccnactt 360

ctaatgttat gaatgggctg gagnancctc nacntgagtt tnnwaaggnt caacanccaa 420

trgnaantgt amccgactct aaattccaac cnataat 457

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<210> SEQ ID NO 17
<211> LENGTH: 373
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(373)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 17

atctgtgcta ggtagtgtac taatcattca gtttatctca tttaatctnn atgnaactct 60

aagtcattcg ctntgancna cacataacag atctcgcaac tgnagtttag cgaggccagt 120

taatttkcca aagntcataa tnctaagnag ttctagnatg gagattcmaa gtccnactgt 180

ttagtcaaga gaccctactg ttaactagta cctttacact actaactggg taanccataa 240

ncaattaatg ataaagattg agattactkc cacattctca ctggttataa attaaaacnt 300

caaataaaaa ntcttggcac ttctatggta atatttttat taggataaac tttcaagnag 360

tggatnctag gtg 373

<210> SEQ ID NO 18
<211> LENGTH: 422
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(422)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 18

cccacactgn tgggccatgg aagccatgag tgtaccacat ggccctgtcc cactggccac 60

agtngattgg ttggntcggg agtagtcacc tgattcaagn tgggccaatc agatcctacc 120

tccanggggt tnggaattag aaaacagtga ccctagytag tntaggcnac ttgaactgga 180

gggcccatac attcaggagc cttatggggc catgtacaca tggaagcagg aagantgaag 240

gagggagaag tagaggccag aaacccacct gggttcctgt ttcccaatgn taagtccctg 300

ccatgtycct gctcttcctg tggttnggat cttcaaaggt tgctcaaatt nggggcagtg 360

gccctggcag cttttcaaat cctycccatt tttattgaag ctgaaagacc cttgactaga 420

ac 422

<210> SEQ ID NO 19
<211> LENGTH: 395
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(395)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 19

attgttattt ttcgtcacta cctccccggg tcgggagtgg gtaatttgcg cgcctgctgc 60

cttccttgga tgtggtagcc gtttctcagg ctccctctcc ggaatcgaac cctgattccc 120

cgtcacccgt ggtcaccatg gttaggcacg gcgactacca tcgaaagtta atagggcaga 180

tctcgagaat tctcgagatc tccntcmaat tattacttca nttkcggtag tgatcagnac 240

naggcagttc tattgatttc tctcctttca ttctgagttt ctccataaat taattggacc 300

taatcatgtt tknaatcctg tcttttaggg ggnanttgna ctntcaagtg tttaaaggga 360

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gggncggagn atgattntgg attggagtga gagca 395

<210> SEQ ID NO 20
<211> LENGTH: 487
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(487)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 20

cagantttct gggtnaaaag gacctnanac ataatatagt ggacttncaa taaacactta 60

ccaaatggan aaatgaaccc ctggtcaccc cgatctcact agtncctncc ctgaaacccg 120

ananatctga gtccttttct cctttactaa cccttnctcc aatcctgctc atgggaatta 180

angntgtaaa atangcctgg ggnacctcgg rcctctnccc tgggntctgt gggtgggagn 240

actgtggaag ccgtwtcaat cgcccccacc tatgagagcc tttctncagg gccagccatg 300

aacgtccccc atgtnatcag natctncagg ctactgctgt ccttcytgga twtttaacct 360

ggrggcgggc cagggacaga aaarggaggt ggcaagatcc ttgaacaaaa ggagctataa 420

aagggcgttg ggggaagcaa ggcaaacggc agattaaaca agcaggcacc tcaaggaaac 480

gtgacgc 487

<210> SEQ ID NO 21
<211> LENGTH: 500
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(500)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 21

ctcgagatct ggcccatcat ttagttttat ngcttgnagt ntntagnaga taaaacatcc 60

acgtggatct nctcttagag aaatcaanta ctttaggnat ntgatagtca gagantggnt 120

atcaaatnga aaggnatntn ggtngancag ttagttngyn ccnttngnng agaccactgg 180

gntgtngasa ccagattcmk gggtncnaat cttanggtaa tctnagagcc aacacatggg 240

tcatnttats ccccaaactt agccacatct bgtggggyta tggngtcacc ccaagagcag 300

gaggagcatg gntggatgga aatccatctc caccactgga accccaawtt ctgaatgnat 360

cacctgttag agtttcttgt ycataaaata gcagggaatt taggaattta gtttttttt 420

aatagtttgg gccttttatc cacactctca ggagcttagg atacttttct ccttcagctc 480

actctgaaac tccctctgga 500

<210> SEQ ID NO 22
<211> LENGTH: 406
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(406)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 22

tcgagatctg tggtagtnac atgatattct ggcamctact ttcattatca cctttattaa 60

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aataaattta aagaaaaatg gcagtatgtt tctgtgragn ccacgagtac tcattttaaa 120

ggactcmaga gttncagrna agtaaaaagr aaagagtaaa atcattttct aantytywyy 180

ttccagaaat aacgatgttg agcattaagt ggacttcatt tcatactctt tcmmagntta 240

tgtaggcata wawatgtgtg tgtatataca tatatatggg tacatcctta gagaagttgg 300

ctggctagat agacacacnt naaaaatggr atcatactct aatkccattt nnantttana 360

aaatacatat tcaganccnc tgtncttata nacagagtaa ntgaaa 406

<210> SEQ ID NO 23
<211> LENGTH: 289
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 23

gacccagtaa aacttatctc atgagcataa ggctgaatgg gattgacagc ctacagaacc 60

cggattttat catgagggca ttagtggggg ttgggggtta ggtactgaaa gtttaaggag 120

gtgaaaggaa agcaacttgt gccttacagg gtcaagctag gtcaaggaaa ttcccaggag 180

cgtgtggaag ctctctacct gataggtgag ctcaagctta tgaccgccca agcttctccc 240

caagcttccc ttccactgct tcctcttgat tgacttccac agcaaggtc 289

<210> SEQ ID NO 24
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(367)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 24

ccatcaggat ttactgagta aaaatctcag gtnttaacca tgcccctaaa atgtgctatn 60

ccaaagagga acaggttact tgggaggaaa aaagctgcct gggnaactcc ccncaaatgt 120

ttattttaaa taaaaatggt ngatggaaat attttntaaa agaacttggg gtntaatatg 180

gnatactgcc catcaaacaa aaaaggaaat aaaacttcnt tcccatttat aataagttnc 240

ccacccttta ctatcaagat tacaacttat tgacctttta tgctngctng gttttttgg 300

gactgcctaa tccaatgttt aaattttcta ngtctgnatt tcaatgtggg taggagtnat 360

ttttcaa 367

<210> SEQ ID NO 25
<211> LENGTH: 425
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(425)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 25

gagtatctga caggtaagat tgctttttaa agttgtttta aatgcattac atgactgaga 60

aaagaaaaat gcacatttta ttgttgcagt ttaaaatttc atttngngtg aaactaaacg 120

tgaaacaaaa gggataaatg tgttttgntt ttgttttggt tttacctgtt tggggtattt 180

ttttctgagt ttgtgtagaa acccgtgtgg ntacactggg taatcttgtc agggntacma 240

-continued

amcttgggtc ttgantttgg ttanttggnt ttanttggtg nacccatgta cttgctcttc 300

cntcccagaa acatagcttg gtaggcnagg gttaanccag tgtcggcgan cccatgtccc 360

tancacagca tcttgtaagt ttaatgcaca atcgttccnt cccaggatgg anttatcatt 420

ataaa 425

<210> SEQ ID NO 26
<211> LENGTH: 2377
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(2377)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 26

gagaggcgca ggagccacaa ataaagcaag agccagaatc agaagnggag gaagaagaaa 60

agcaagaaaa agragraana cgagaagaac ccatggraga ggaagaggan ccagancmaa 120

agccttgtct gaaacctact ctgaggccca tcagctctgc tccatctgtt tcctctgcca 180

gtggnaatgc nacacctaac actcctgggg atgagtctcc ctgtggtatt attattcctc 240

atgraaactc accagatcaa cagcaacctg aggagcatag gccmaaaata ggactaagtc 300

ttaaactggg tgcttccaat agtcctggtc agcctaattc tgtgaagaga aagaaactac 360

ctgtagatag tgtctttaac aaatttgagg atgaagacag tgatgacgta ccccgaaaaa 420

ggaaactggt tcccttggat tatggtgaag atgataaaaa tncaaccaaa ggcactgtaa 480

acactgaaga aaagcgtaaa cacattaaga gtctcattga gaaaatccct acagccaaac 540

ctgagctctt cgcttatccc ctggattggt ctattgtgga ttctatactg atggaacgtc 600

gaattagacc atggattaat aagaaaatca tagaatatat aggtgaagaa gaagctacat 660

tagttgattt ngtttgttct aaggttatgg ctcatagtnc accccagagc attttagatg 720

atgttgccat ggtacttgat gaagaagcag aagtttttat agtcaaaatg tggagattat 780

tgatatatga aacagaagcc aagaaaattg gtcttgtgaa gtaaaacttt ttatatttag 840

agttccattt cagatttctt ctttgccacc cttttaagga cttkgaattt ttctttgtct 900

tkgaagacat tgtgagatct gtaatttttt ttttttgtag aaaatgtgaa ttttttggtc 960

ctctaatttg ttgttgccct gtgtactccc ttggttgtaa agtcatctga atccttggtt 1020

ctctttatac tcaccaggta caaattactg gtatgtttta taagccgcag ctactgtaca 1080

cagcctatct gatataatct tgttctgctg atttgtttct tgtaaatatt aaaacgactc 1140

cccaattatt ttgcagaatt gcacttaata ttgaaatgta ctgtatagga accaacatga 1200

acaattttaa ttgaaaacac cagtcatcaa ctattaccac ccccactctc ttttcatcag 1260

aaatggcaag cccttgtgaa ggcatggagt ttaaaattgg aatgcaaaaa ttagcagaca 1320

atccattcct actgtatttc tgtatgaatg tgtttgtgaa tgtatgtgta aaagtctttc 1380

ttttccctaa tttgctttgg tggggtcctt aaaacatttc ccaactaaag aatagaattg 1440

taaaggaaaa gtggtactgt tccaacctga aatgtctgtt ataattaggt tattagtttc 1500

ccagagcatg gtgttctcgt gtcgtgagca atgtgggttg ctaactgtat ggggttttct 1560

tattaataag atggctgctt cagcttctct tttaaaggaa tgtggatcat agtgattttt 1620

ccttttaatt ttattgctca gaaatgaggc atatccctaa aaatctcgga gagctgtatt 1680

taatgcattt ttgcactaat tggtccttag tttaattcta ttgtatctgt ttatttaaca 1740

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aaaaattcat catatcaaaa agtgtaagtg aaaacccccct ttaaaacaaa acaaaaaaat 1800

gaaataaaat taggcaaatt gacagacagt gagagtttta caaacatgat aggtattctg 1860

ctcggcaatt tgtaagttta catgttattt aaggataaag gtaaatcatt caaggcagtt 1920

accaaccact aactatttgt tttcattttt gtcttgtaga aggtttatat cttgttttac 1980

cttggctcat tagtgtttaa aaatgtactg atgatgtgct tagagaaatt cctggggctt 2040

tcttcgttgt agatcagaat ttcaccaggg agtaaaatta cctgaaaacg taagaagttt 2100

taaacagctt tccacacaaa ttagatgcaa ctgttcccat gtctgaggta cttatttaaa 2160

agaaaggtaa agattggcct gttagaaaaa gcataatgtg agctttggat tactggattt 2220

ttttttttt taaacacacc tggagaggac atttgaaaac actgttctta ccctcgaacc 2280

ctgatgtggt tccattatgt aaatatttca aatattaaaa atgtatatat ttgaaaaaaa 2340

aaaaaaaaaa aaaattcctg cggccgcaag ggaattc 2377

<210> SEQ ID NO 27
<211> LENGTH: 489
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(489)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 27

attggagctc caccgcggtg gcggccgctc tagnaactag tggatccccc gggctgcagg 60

aattctcgag atctccccca agtaaatgaa tgaaaaaaag aacagcaaca atagagatga 120

tataataagc caggcatgga tgaccttata gcaccctgta tttatacaga accaccagga 180

ggatagtcat gacaacnatg acactgatca tgatnccagc attcagaatt gagtncaggg 240

ctctctggcc cacagtctcg gtatcttctg tgnatggggt atagattarc tgtccatcct 300

tccgggnata aaanctgact gacttaatgg tanccacgac caccacccat kcagagagtc 360

acagggacma aagagcatga tcaacatgct tggcnccata tttcaatntc anctcctcat 420

cttcttcctc atcttnctcc accacctncc gggagttaac cctggggtcg tccattagat 480

aatggctca 489

<210> SEQ ID NO 28
<211> LENGTH: 2307
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 28

agggtgcttc agtgtggctg acacagcagc atggtcttga caagttttct tcatcctacc 60

acaaaatccc agttggtaat agagacttta ctcctaccta tcaaaaccac aaaatgtccc 120

attaggggggg gacatgttgt acatgttagg atcattcaaa taaccaagat tataaggtga 180

ggaaagatgc ccctaactga ttcttttgtc tctcatcttg ttggttccag ggaccgagtg 240

gggtcaatct tctggtsstg cctctccagg tctcttccag gccggtcata gacgtactcc 300

ctctgaggcc gaccgatggt tagaagaggt gtctaagagc gtccgggctc agcagcccca 360

ggcctcagct gctcctctgc agccagttct ccagcctcct ccacccactg ccatctccca 420

gccagcatca cctttccaag ggaatgcatt cctcacctct cagcctgtgc cagtgggtgt 480

ggtcccagcc ctgcaaccag cctttgtccc tgcccagtcc tatcctgtgg ccaatggaat 540

-continued

gccctatcca gcccctaatg tgcctgtggt gggcatcact ccctcccaga tggtggccaa 600

cgtwtttggc actgcaggcc accctcaggc tgcccatccc catcagtcac ccagcctggt 660

caggcagcag acattccctc actacgaggc aagcagtgct accaccagtc ccttctttaa 720

gcctcctgct cagcacctca acggttctgc agctttcaat ggtgtagatg atggcaggtt 780

ggcctcagca gacaggcata cagaggttcc tacaggcacc tgcccagtgg atccttttga 840

agcccagtgg gctgcattag aaaataagtc caagcagcgt actaatccct cccctaccaa 900

ccctttctcc agtgacttac agaagacgtt tgaaattgaa ctttaagcaa tcattatggc 960

tatgtatctt gtccatacca gacagggagc agggggtagc ggtcaaagga gcmaaacaga 1020

ytttgtctcc tgattagtac tcttttcact aatcccaaag gtcccaagga acaagtccag 1080

gcccagagta ctgtgagggg tgattttgaa agacatggga aaaagcattc ctagagaaaa 1140

gctgccttgc aattaggcta aagaagtcaa ggaaatgttg ctttctgtac tccctcttcc 1200

cttacccccc tacaaatctc tggcaacaga gaggcaaagt atctgaacaa gaatctatat 1260

tccaagcaca tttactgaaa tgtaaaacac aacaggaagc aaagcaatgt ccctttgttt 1320

ttcaggccat tcacctgcct cctgtcagta gtggcctgta ttagagatca agaagagtgg 1380

tttgtgctca ggctgggaac agagaggcac gctatgctgc cagaattccc aggagggcat 1440

atcagcaact gcccagcaga gctatatttt gggggagaag ttgagcttcc attttgagta 1500

acagaataaa tattatatat atcaaaagcc aaaatcttta tttttatgca tttagaatat 1560

tttaaatagt tctcagatat taagaagttg tatgagttgt aagtaatctt gccaaaggta 1620

aaggggctag ttgtaagaaa ttgtacatra gattgattta tcattgatgc ctactgaaat 1680

aaaaagagga aaggctggaa gcatgcagac aggatcccta gcttgttttc tgtcagtcat 1740

tcattgtaag tagcacattg caacaacaat catgcttatg accaatacag tcactaggtt 1800

gtagtttttt ttaaataaag gaaaagcagt attgtcctgg ttttaaacct atgatggaat 1860

tctaatgtca ttattttaat ggaatcaatc gaaatatgct ctatagagaa tatatctttt 1920

atatattgct gcagtttcct tatgttaatc ctttaacact aaggtaacat gacataatca 1980

taccatagaa gggaacacag gttaccatat tggtttgtaa tatgggtctt ggtgggtttt 2040

gttttatcct ttaaattttg ttcccatgag ttttgtgggg atggggattc tggttttatt 2100

agctttgtgt gtgtcctctt cccccaaacc ccctttttggt gagaacatcc ccttgacagt 2160

tgcagcctct tgacctcgga taacaataag agagctcatc tcatttttac ttttgaacgt 2220

tggcgcttac aatcaaatgt aagttatata tatttgtact gatgaaaatt tataatctgc 2280

tttaacaaaa ataaatgttc atggtag 2307

<210> SEQ ID NO 29
<211> LENGTH: 343
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(343)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 29

ggcagctatt tacatggcct cacaggcatc agctgaaaag aggacccmaa aagaaattgg 60

agatattgct ggtgttgctg atgttacaat cagrcagttc tatagactga tctatcctcg 120

agccccagat ctgttcctta cagacttcma attkgacacc ccagtggaca aactaccaca 180

-continued

gctataaatt gaggcagyta acgtcmaatt cttgannacm aaacttkncc tgttgtacat 240

agcctatacm aaatgctggg ttgagccttt cataaggnaa aacmnaagac atggntacgc 300

attccagggc tkgantactt attgcttggc attcttgtat gta 343

<210> SEQ ID NO 30
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(363)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 30

aaagggctaa ccagccactg caccaaaatt agtccttaca ttataatact ctggccattg 60

gaagagaaaa atgggaaaat tcaacaattt gaaagactat gatccctctg gctcatgatc 120

tactgaccag aatgaagtcc tgaaggattt ccttctgtta tgttatctac ccagctaatc 180

tcaaacaaga ggagctggaa agaacaaagc cccatgaagc taccctaga cccagaaagc 240

caagaacagg gccaagaaaa tgaacagcag acaagcctga aatagaagtg gnacagacat 300

gtggnaagac caagtacacc cagttnggtg gtaaagattc cgatatcaag cttatcgata 360

ccg 363

<210> SEQ ID NO 31
<211> LENGTH: 362
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(362)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 31

agtacatggt ttcttgncca ccccasccac ctttccccat ctctaccggy tgatagtctc 60

tcagntagta gacctttttct ngtttagrca gggccacntt tttaaaaact ccagacgggt 120

accctccatg tkgmaggcga cgtggccctg gatcactcaa ctgantgtca tnkgantggt 180

gcccccagag tgaggacaat ggtgnagccc tcctaaggcc ctnnctgagt gtccctcctt 240

catgaagatg attctgaggn ttcccaggcc tncacccttc ttkgaaarcc catagnagtt 300

catatgnact nctctnctat gctcaccaaa ctctnnccttc atcatacttg ggggatgtgt 360

gt 362

<210> SEQ ID NO 32
<211> LENGTH: 475
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(475)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 32

gtgcatgtaa ttacagttac gatatatgaa acgtacaaaa tattatgagt atataatatg 60

gggagactta atctagtttg ggggatcagg gcacatttct ctaagaaagt gacatttgaa 120

ttgagctctg aaggataaat agacattacc cagaagaata aaatgatggg gaagaaggag 180

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gacattttcc gtagatttcc agtggccccn cttgatccct tatccactca tcactnagga 240

ggatattaaa tkctatagaa atggragraa gacmmaaaga gaccctnata tctcgagagg 300

atccagcmaa attccaagag acacaacawt aagaaactng gaaggaagag aaaaggcmmn 360

nnaggnaaaa gaaagacaag gaaattnwnn nagnacggag agaaagagag agggagcgtn 420

naagggnacg agaaaggcga gnacggggac gagaaagggn aagagnacgt aaacg 475

<210> SEQ ID NO 33
<211> LENGTH: 346
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(346)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 33

ggaaataaat gagatctcag tggtggtatg gattggactg atctctgtaa ctgtgtntgg 60

aaaaaggacc ggaaaatgaa agccagatcc cagtaagggg tagagagggg ccaagagaac 120

tgaacatctg ggctgccgga gaaatcaaag tctaggaagt aagaggtaag agtgtactac 180

aggggacata ccccaatctc ttggttccct ccctctnnct tcctctccca gagacccagg 240

tccctgggac tatnttggat ctgtctctga agctgaaaaa caaaaggcag aggagacagt 300

cggntctaag tgaccaatct caagccagct tggtcagaan tcctaa 346

<210> SEQ ID NO 34
<211> LENGTH: 433
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(433)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 34

aaatccagtg caggcaacat tatgtggaaa tagaaacagg gctcctgcta ggagattgan 60

attctggctt tcctttggaa cccctcactg actcatcgcc cctgaancag ganccancag 120

gtnccaaggc tcccctgctc ctntccctnc cccagggcga gataggaarc cggaarcctg 180

ggcaggctga rcccanccga ctggaaccag ggnagancct gtgggtgggt ggnagggagg 240

gaaggaggcc agattcctcc agaactgggg ragagaacag gttttggaag ttgggggagg 300

gtttgggttt cacagtgatg gtttcatgan accctggagg gttncacact cctggtkcan 360

ttttgntant cgtnctttga anacarnccg cttcctttca accctccncn taaaaagttt 420

tgatntttta agg 433

<210> SEQ ID NO 35
<211> LENGTH: 350
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(350)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 35

accaagagcc cccagtttat gntaactctc atgacaaaca caattttagt acctctcact 60

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accaactatc caggaaccag gantcaccta ttactacggt tccagcagaa tgggaatccc 120

attctcggat atccagggta aatccctgac catgtgagag gaatcctagt gccccaacaa 180

cctcaccccc tgactcctcc tcaanggctc tgccaagtca acaaaaaaat cctctacatt 240

tacactatct gtaaagccaa agaccagcgt caacctaaat gtccatcaat aagggaatgg 300

ttggataagt aaaaattatg cagctgtagg aaggaatgaa gaatgtctat 350

<210> SEQ ID NO 36
<211> LENGTH: 512
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(512)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 36

aaagggaaca aaagctggta ccgggccccc cctcgaggtc gacggtatcg ataagctgga 60

tatcgaatcc tcgagatcta cctaaaaaaa aaaaattaac ttcccaaatg tgggagtcta 120

ctctgttccc tcctngtntt tattnctgtn tactttycta anatggttaa aatgtgtaan 180

caatatgtgt cctttnactn kggkgtgaac atttttycta ttataaatyc twagaaaata 240

ttnctatggn tatgagatat tkgattccaa gtgcctkgta atttactyct caaatgtccc 300

tgatgtkgga nattkgttnc tagtgttyca ctatttaaaa aaacagnaat atctgtctnt 360

atgctnagag cttntycagt ttycaaatta ttnccttagg gtaaaatcct agaagtagaa 420

tttttggggc aaattatcta catatttata attgtcttgg tattccaaat ctcgttttcc 480

aaaagcttat atcaatttgt acttaacacc ag 512

<210> SEQ ID NO 37
<211> LENGTH: 450
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(450)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 37

atttaagatg actgggggtc tctncctaat cccatactcc actggagagg anaagtggga 60

aaggttggtc tagttarggt ngntggggac cctcccaaga gctgnagaag cagagataag 120

nagagcctnc tnctaaatcc acatggncct yccaaggntc tcatcctcta ggacctacca 180

ctnctcagtc tacttacttg tctyctgana tgctttctng aggggnagaa aacaaaggaa 240

gagtaataac aagcagnaga aactgcagag aatgnaaaat aagtccatag gagaatgttg 300

naaatagaat catccncctt tacatattgt cactccagga aaactgccaa gaaccactca 360

ttcctctaga tacamttcct gtaggatccy cccagacttc ctcccttaag cacgtcagta 420

ttctccttat tctcccttca tttcaaccct 450

<210> SEQ ID NO 38
<211> LENGTH: 766
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(766)

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<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 38

cgagatctgc cccagcccac atttcctttg ttgaatgagt agagaagact gagaagtatc 60

actcacccgt gatgtggttt gtccctttc cagccagtgt gttggtaata aaagtcacct 120

ttcagagctt tggtccccgt aatgcccgtc tttcctgtgt ccaggaataa cctttgntac 180

taggcagtcc tctgaaagat ttgtagaagg ttaaagtgga aagggacttg gaagctcata 240

gaatccatgc ctcttctttt agcatcaagg aattagaagt cctgagagat gaagaatgtt 300

gtcttcccaa ctcaaaccca tttcttgaag ccatttccct ggttactgna ttggccacaa 360

cccttccccc ttgntatcct catcctgcta atgctgtttt taatggcctg ccagtctgga 420

tttgtctttg gcaaccaaac aattttgctt cacaagattc ctacttaagg gaagagaggg 480

gctcctcatt tntcacttgt acaagagcag ggctggtcag ctttacacag gtgtcagatg 540

aaccgtcaca anccagantt ncatgttggc ctcaggaggg cttcnaggtc caacatctcg 600

acgtaaggag cgttcccagt tctttcatgc tcagataaca gtnctaactn cagctgtttc 660

atcccnaatc cctanttgag gtcttaacat ctattccatt ttkccnacma gggttatnct 720

gttaaccctc tncaccagan ttaganctga ctgatncact tcctag 766

<210> SEQ ID NO 39
<211> LENGTH: 327
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(327)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 39

tcatacttgt atagttcknt aagataatca ctctctcact cagacatnng gngrarngcc 60

cntcgatcac ttggganagg ngacttgcma tgtttaatga ttgtcanccm nanaantaag 120

ctnacagggc aaaaacagcc tyangtcagt tctntctccc taatcctcta graknaaatc 180

nnawrntrnn actctgnntc tgtgccatna nanatnttnc anttgtattt atgnactcca 240

catngagtac acctcactaa wtntnctnct gggnaacncc cscmccantt tttnnttgnt 300

gananacarc aatgctggca tacngtg 327

<210> SEQ ID NO 40
<211> LENGTH: 431
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(431)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 40

ccagactttc ataactngtg ttattatgaa gattagagtn ctgaagctta ctggattaga 60

agagnacgag ggggtagctg ccccaatata ttctaatttc tctkgaggac caccaaatng 120

gmagagtgtc tctgataggg aaaaggaaga gttggaaggn atcttagcct ctagganaaa 180

agaaccattt ttattggcca ccaaagttac atctagtkgc ctacaaattt atntccaaac 240

tccttatcct gccaattcag ggtcctgnaa actgatgcca aactatagtt tagtctncta 300

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tcacatgact gcattataca tacccaatta tctgggmaaa cagacctgat ccaaacacag 360

ttkggtnctt tccttncctt nccttkgttt agcctgtycc gtctactngg ggtgtcttkg 420

atttgctcca g 431

<210> SEQ ID NO 41
<211> LENGTH: 276
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(276)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 41

ttttttttcca ccagacttac caaattttag atgnatggaa gaactgtaaa tncccataaa 60

gntaatctat ncatngaccc ccaccattat gatagagatc atntggtgan taatgaaaga 120

tgaaactctc agctgggaaa gtaanaagga ataggatgta agtatgagct cctgtttttt 180

attatnttta tggatgcccc ctcagaaaaa tatgnaangg ggtaactgac tnggaaatgg 240

gtnttttatg natagtaagt cccactcacg aggttt 276

<210> SEQ ID NO 42
<211> LENGTH: 270
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(270)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 42

tcgagatcta aagcagatgn agactttnca cnaaataaat ttactgcttt tttyctgtga 60

nataagttnc gagaaggaaa gctttkgatt nctrnatgag tycagtggat tatyctnagn 120

actagagtkg nkgtkgaagn catggnacat ttatatagwt ywttcagttc tacactaaat 180

gatggaagaa tgagaaatcc tatatgacaa atagaaaagt ycatyctyca taattgagaa 240

cattgagcag ttggattacc aagatctcga 270

<210> SEQ ID NO 43
<211> LENGTH: 580
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(580)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 43

cttagtttta gactagtttc attatactac cagtttctaa tatgttggtt ttttattcac 60

tatttgatat atttgtttta atatatgttc ttgttttagc aggtaaaaga atcataacaa 120

atgtttttaa aagaacatta ttattcttta ataactgtct ttttatgcat ttggcatgcc 180

aacttttttc attaacatct tgggtatttt ataaaaagag ggaaagctca atgtttaaca 240

ggtagctttt cttaggagct aaattaaata tttaacaaat ctccttccct tcnccccttcc 300

ccatccctca aagnatgggt gnanttatct ttaacttttg ggctngcatc cntgnaagct 360

tatggntant catagtctna cmaaactagg gtcaccnaac ttggcagcag aaataatcta 420

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gtcttactgt gataactacc caattacttt attatttttc cagttncagt tccaaatgtt 480

ttgtggnaan aatttttnct gtttgtgatt ttccaagctt agaggggggaa accaactttc 540

cagtgttgga gagcactgna tagtttatgn attgtgtaaa 580

<210> SEQ ID NO 44
<211> LENGTH: 348
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(347)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 44

tgtttcttaa nacagaaaaa aatttactga tnggacattg ttctaagtgt attattgtat 60

taaatggatc atttaattta atcttcataa ctgacatagg agttgagtaa cttgtgtggt 120

caaatagcta gtaagtgatg agtaggctgg gcgcagtggc tcaagcctgt aatcccagca 180

ctctgggagg ctgaggcagg cagatcactt gaggtcagga gtttgagacc agcctggnca 240

acatggnaaa acctcgtctc tactaaaaat acaaaaatta gctgggcgtg gtgggngcgc 300

acttgtagnc ccagntactc ggaaggctng aggcaggagg aatcgctt 348

<210> SEQ ID NO 45
<211> LENGTH: 430
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(430)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 45

gctcatcatg cttcacgggg gaggctgtgc gggaagaatg ctcccacaca gnataaagaa 60

tgctcccgca caggatagag aatgcccccg cacagcatag agaagccccc gcacagcata 120

gagaatgccc ccncacagca tagagaagcc cccgcacagn atagagaatg ctcttcacct 180

ctgggttttt aaccagccaa actaaaatca cagagggcaa cacatcattt aagatagaaa 240

tttctgtatc ttttaatttc tttcaaagta gttttactta tttncagatt ctatttcttt 300

actagaatta agggataaaa taacaatgtg tgcataatga accctatgaa acaaacaaaa 360

gctaggtttt ntncataggt ctncttccnn attgaatgaa cgtctntcct caaatttanc 420

cccccaggga 430

<210> SEQ ID NO 46
<211> LENGTH: 402
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(400)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 46

caaaccctat gngaaatgga aaggaaacta ttctaaagca taaaaggtag aaatatatat 60

accacccatc aagaaagatt atttttgntg aactcaagtc accagagtgg ctaaagccca 120

gtagaatgga aatgattata tggaaggtga ggccaacggg accagaacat actgtgatag 180

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acagnaagga gctgtctatc ttctattctc ccacagaagg aggtgactaa gtcanctgcc 240

caagcaatgt tatatctgca attgatgtnc agcagtacaa gtctgaacaa cttggattgg 300

ntgattaant gtccnacant aaacatacaa gtcntaatag ctatctctat atagtctttg 360

ggtntttaca aggcactgnc acatnatctc acctattcct cc 402

<210> SEQ ID NO 47
<211> LENGTH: 500
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(500)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 47

agnatccaga attgagtgna gngttctctg gnccacagtc tcggtatctn ctgtgaaatg 60

gggtatagat tctacaataa aacaaacaca nnggccctag gtcagtgtta atggagatca 120

ccanccacat taccacctcc aacacagaat tttctttttc ttaatncaat ncgtntctta 180

taagtcactt tncccaact caccaatcta gntaagaatt tttaccctga gaaaaacagc 240

tacactctaa aattgctnca aagaaaatgt ctaacatntg gaaagaagga cttaacatgt 300

gangnagaca ctggctccat ctagngggtg ctttnttttg aaataattat aatnccncat 360

caaattttng ggggntacag cttattagga acttgttata gaaccagatt ctgccacaga 420

anccacgtgg gttgacaagt ggttgncaga agaaaggtaa tatggcttat nattagggnc 480

tcncatctgc agagtaattg 500

<210> SEQ ID NO 48
<211> LENGTH: 460
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(460)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 48

aaaatgcttg anncaaatgt catctagttc catctctacg actctcatgg ggtccaaaga 60

agagttttan ttgagtttta gaatgtgaag ttgtgaagtg tctgaaaaac tacatggtgn 120

tctgaaagnc aaacttttag ccttgggggga gagcatctaa gacagnaggt gaagggnagg 180

ggttagaact agagggattg aagaatatta tccatatagg ttagggttag gtnnggcaac 240

gttttataga acaaacattg gcaagctaca gccacaggcc agatctgtct nctaccttcc 300

cacaaaggtg taataacaaa gttattcaca aatgtgtgaa taaactnnca ttggaaagtg 360

cccacgctcc tnggtttata cattgtctgt ggctgctttc acactacagt agcacaggtg 420

agtgtntgca ctggagacca tatgccccat agagctttaa 460

<210> SEQ ID NO 49
<211> LENGTH: 372
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(370)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

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<400> SEQUENCE: 49

atcaagcaac agtgtgttat gcctatactc catgtttata tgtgtgtatt aaaaaatgta 60

tttngtatat atgtgtatgt ataagtgtgt gtgtgtgtat gatgattctn ctcccgnttt 120

gaaggtgaaa gaaagcacac ctttatttaa gcataaactt tgggtttcan gatactgtct 180

ggaaaaatga tttatctccc actttgaaat tccaaaatac gtacatatat ttttttttc 240

ttttcttttt tagtttnagg gtcttgctgt gttgcccagg ctggagtgca gtagtgtgat 300

catagntcac acagnctcta actcccaggn tcaagntatc ttcctgcccc agnctcctga 360

gtagntggga ct 372

<210> SEQ ID NO 50
<211> LENGTH: 500
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(500)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 50

caaaaaatca aagggaagnt ggaacccctg cccacctctc cattccccat tctgctggtg 60

gtgnctgctc ttcctcacag tacctcctga aaagttcaga attcagttaa tacagaatta 120

ttgggttgat tttcaacgtg tagtttaaga tgaagagttc cgnttggttt aaaccacttc 180

acctaacctc ttggtaacgg tagtcctgag agttcgcagt gtcantgaaa atcgtcctgt 240

gaccacgcgt caagctgctg atgggggaca gaaacttccg ggnctatcat atctccttga 300

nctcggccct caaatctggt agtttctgca ccgagggaca cagtccactg cgatgaagta 360

tgttcaaaat cgntttcttt agggaactcc ttccaaagtc caatagtgna aggtggtcaa 420

ggaaggattt ggaaggaagn tgnaaaagtc agncgggaat cttgatttgg ntagntgtgg 480

ananaggaaa tcacttggcc 500

<210> SEQ ID NO 51
<211> LENGTH: 105
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(105)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 51

ggaaagaggt ctcctaacac ccagacagtg taaaaatcca gtttttcttc cttttggnng 60

gagacagagt ctcgcactgt agctcaggct ggagtgcagt ggcac 105

<210> SEQ ID NO 52
<211> LENGTH: 387
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(387)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 52

agtcccagct actcaggagg ctggggcagg aagatagctt gagcctggga gttagaggct 60

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gtgtgagcta tgatcacact actgcactcc agcctgggca acacagcaag accctaaaac 120

taaaaaagaa aagaaaaaaa aaatatatgt acgtattttg gaatttcaaa gtgggagata 180

aatcattttt ccagacagta tctngaaacc caaagtttat gcttaaataa aggtgtgctt 240

tctttcacct tcaaagcggg agaagaatca tcatacacac acacacactt atacatacac 300

atatatacaa aatacatttt ttaatacaca catataaaca tggagtatag gcataacaca 360

ctgttgcttg ataaaatata gggatcc 387

<210> SEQ ID NO 53
<211> LENGTH: 380
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(377)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 53

tatatttnat caagcaacag tgtgttatgc ctatactcca tgtttatatg tgtgtattaa 60

aaaatgtant ttgtatatat gtgtatgtat aagtgtgtgt gtgtgtatga tgattctcct 120

cccgnnttga aggtgaaaga aagcacacct ttatttaagc ataaactttg ggtttcnaga 180

tactgtctgg aaaaatgatt tatctcccac tttgaaattc caaaatacgt acatatattt 240

ttttttttctt ttctttttta gtttnagggt cttgctgtgt tgcccaggct ggagtgcagt 300

agtgtgatca tagntcacac aggctctaac tcccaggntc aagctatctt cctgccccag 360

nctcctgagt aggtgggact 380

<210> SEQ ID NO 54
<211> LENGTH: 521
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(521)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 54

ctgcagtaag ccacgttcat gccactgtac tctagcgtgg atgacagaga gagatcctgt 60

ctttggaaga aaaaaacaaa aagaaaaaaa aaagagtatg gccatggcct tataatatag 120

aaggggtcac atattaatct ctgaaaatgg atctcttgtg ggctttcata caaggcaaca 180

gccacagagt acgtacctga aagctgcctg ggnttaatgg ctggnagtat gttctaactn 240

gttcaggnac ccatgtcacn actggtggtt acagaatgtg aatctcacac tgtccnaaat 300

cggttttatt tttaaaanga ataattctan tacattacct tataaaaagt aggtaaccta 360

attttggntt ttaaaagtga attgagggca gatgcaagtg gntcacacct attaatccca 420

aataccttgg agagggcaag gtaggaggat tggttggagc ccaggagtcc aaagaccagg 480

ctagggaata ttgnaagaan gtcctctcta caanaaanaa t 521

<210> SEQ ID NO 55
<211> LENGTH: 516
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(516)

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<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 55

ctgcangaag cttttnttnc ttttnggngg agacagagtc ttgctgtgtc ancccaggct 60

ggggtgcagt ggnacagtca tagctcactg caaccttgaa ctccctggnt catgcgatcc 120

tcccacttca gcctctcaag tagctagaac tacaggtgtg caccaccatg cctgactaac 180

ttgtttattn gngggagaga gaacgntctt gctatattgc ctaggctggt cnttgaactc 240

ttgggntnca agcaatcctc ctaccttggc ctctncaagg tanttgggat tnataggtgt 300

gagccacntg catctggcct caattcactt ttaaaatnca aaattaggtt acctactttt 360

tataaggtaa tgtattagaa ttattcttnn naaaaataaa accgatttgg gaaagngtga 420

gantcacatt ctgtaaccac cagtggtgaa atgggtcccc gaacaaggta gaacatactc 480

ccagccatta accccaggga gngttcaagt ccgtnc 516

<210> SEQ ID NO 56
<211> LENGTH: 505
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(505)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 56

ggatcctgtt tcttaaaaca gaaaaaaatt tactgatagn acattgttct aagtgtatta 60

ttgtattaaa tggatcattt aatttaatct tcataactga cataggagtt gagtaacttg 120

tgtggtcaaa tagctagtaa gtgatgagta ggctgggcgc agtggntcaa gcctgtaatc 180

ccagcactct gggaggctga ggcaggcaga tcacttgagg tcaggagttt gagaccagcc 240

tggccaacat ggnaaaacct cgtctctact aaaaatacaa aaattagctg ggcgtggtgg 300

gtgcgcactt gtagtcccag ctactcggaa gggttgaggc aggaggaatc gcttggtccc 360

cgggagggag aggttgntng tgnagctgag atcacgccac tngcactcca ggctgggnaa 420

caaaagggag acctttnctc aaaaaaaaat naaaataaaa agtgatgagt aggattggga 480

cccnagacat cttttctcca agacc 505

<210> SEQ ID NO 57
<211> LENGTH: 500
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(500)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 57

ctgcagnctc aaacccttgt cctgggatca aacaatcctc ccacctcagc cttcaaagta 60

gatagaacta caggcatgca ctaccatgcc taatttttta aaaaaaaatt ttttttcaga 120

gatgagatct cactgtgttt cccaggnttg tccggaactc ctggactcaa gcgatcctcc 180

caccttgggc tgccaaagtg ttgggattac aggcatgagc caccatgcct ggccatacac 240

ttttttttt tttttaanca agacggagtc tngttctgtc gcccagactg gagtgcaggg 300

gcgtnnatct tggctcactt gaaagcttcg cctcccaggg ttcatgccgt tctcctgnct 360

-continued

cagcctccca agtnggtggg actacaggna tctgcaccac gnccggttat ttnttgggtt 420

tgnngnaggg acggggtttc accatgttag gcaggatgac ttcggacttc cngacccaag 480

atcaccctgc tcggctccca 500

<210> SEQ ID NO 58
<211> LENGTH: 440
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(440)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 58

gaattccaga cgagcctggg caacacagtg agactctatc actacaaaaa aattttaaaa 60

ttagctaaag ttgatggnac atgcctgcag tcccagctac tcaggaggct ggggcaggaa 120

gatagcttga gcctgggagt tagaggctgt gtgagctatg atcacactac tgcactccag 180

cctgggcaac acagcaagac cctaaaacta aaaaagaaaa gaaaaaaaaa atatatgtac 240

gtntttgggg aatttcaaag tgggagataa atcatttttc cagacagtnt cttgaaaccc 300

aaagtttatg cttaaataaa ggtgtgcttt ctttcacctt caaangcggg agaaggatca 360

tcatncacac acacacactn atcatncaca tttttacaaa tncaattnnn naatacaaca 420

cattttaaca tggggttttg 440

<210> SEQ ID NO 59
<211> LENGTH: 513
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(513)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 59

ggatcctgtt tcttaaaaca gaaaaaaatt tactgatagn acattgttct aagtgtatta 60

ttgtattaaa tggatcattt aatttaatct tcataactga cataggagtt gagtaacttg 120

tgtggtcaaa tagctagtaa gtgatgagta ggctgggcgc agtggctcaa gcctgtaatc 180

ccagcactct gggaggctga ggcaggcaga tcacttgagg tcaggagttt gagaccagcc 240

tggccaacat ggnaaaacct cgtctctact aaaaatacaa aaattagctg ggcgtggtgg 300

ntgcgcactt gtagtcccag ctactcggaa ggctngaggc aggaggaatc gcttgatccc 360

ngggagggag aggttggtng tgangctgag atcacgncac ttgnactcca gnctgggnaa 420

caaangngag atcttntctc aaaaaaaaat aaaantaaaa ngtgatgagt aggatttgga 480

ccccagacat cctntctcca ggacctggna ttc 513

<210> SEQ ID NO 60
<211> LENGTH: 390
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(390)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 60

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gaattcctgg nctcaagtga tcctctcacc tcagcctccc aaattgctgg gattagagtg 60

tgagccactg tgcctagcct gcatatatct atttttaatg actgctaaat ctcattgtat 120

gaaaatttat gtcctagcta taaaatttgn tagcacatgt ttaatttttt ctaatttcag 180

atgttttaaa ctaatatttc ccaaagtata gtatggcatt ttaggtatga tatgatcttt 240

nntcctcttc gtactcattt ttatagttat ggcctgtgca actggtttcc catttatatg 300

aatgatacag agcttcctat taagaaaaag ttcagcttgg ggaaaaaaaa agtgaattgt 360

caacttngag ggaaaaaagt gaattattgg 390

<210> SEQ ID NO 61
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(366)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 61

tcaagtacct ccctgaatgg actgcgtggc tcatcttggc tgtgatttca gtatatggta 60

aaacccaaga ctgataattt gtttgtcaca ggaatgcccc actggagtgt tttctttcct 120

catctcttta tcttgattta gagaaaatgg taacgtgtac atcccataac tcttcagtaa 180

atcattaatt agctatagta acttttttcat ttgaagattt cggctgggca tggtagctca 240

tgcctgtaat cttagcactt tgggaggctg aggcgggcag atcacctaag cccagagttc 300

aagaccagcc tgggcaacat ggcaaaacct cgtatctaca gaaaatacaa aaattngncg 360

ggnatg 366

<210> SEQ ID NO 62
<211> LENGTH: 498
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(498)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 62

aacaccaggg ncatgagggc actaatcata atgagatatg cctgctggag tcgaagtgga 60

cctttccagt gaatggaaat cattcccacc acaccaaaat tccagatcag gagtgnaaca 120

gtaatgtagt ccacagcaac gttataggtt ttaaacactt ccctgaaaaa aaattacaca 180

gattttaaaa gatgtacaat aatttccacc aaaacattat ttagaataat gtgatggctc 240

ccaaacatta gatattaatn tcccaccttt ataattttac cataacctat atcaactgtg 300

ctattattta tttaatnctt ccctntaaat taatttactc tttttttgtt tttgtttttg 360

ngtttggagc cagtgtctca ttttggttgc ccaggcttgg agtaaagtgg gtgcaatcac 420

ggctcaactg nagtctttnc ctccnggaga tcaggtnggt cttccccagg tccaanctcc 480

taagttggtt ngganaac 498

<210> SEQ ID NO 63
<211> LENGTH: 469
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature

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<222> LOCATION: (1)..(469)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 63

taaacaacag ggncatgagg gcactaatca taatgagata tgcctgctgg agtcgaagtg 60

gacctttcca gtgaatggaa atcattccca ccacaccaaa attccagatc aggagtgaaa 120

cagtaatgta gtccacagca acgttatagg ttttaaacac ttccctgaaa aaaaattaca 180

cagattttaa aagatgtaca ataatttcca ccaaaacatt atttagaata atgtgatggc 240

tcccaaacat tagatattaa tntcccacct ttataatttt accataacct atatcaactg 300

tgctattatt tatttaatnc ttccctctaa attaatttac tctttttttg tttttgtttt 360

tgtgtttgga gccagtgtct cattttggtt gcccaggctt ggagtaaagt gggtgcaatc 420

acggctcaac tgnagtcttt acctcccgga gatcangttg gtctttccc 469

<210> SEQ ID NO 64
<211> LENGTH: 370
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(370)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 64

gtttatcaag tacctccctg aatggactgn gtggctcatc ttggctgtga tttcagtata 60

tggtaaaacc caagactgat aatttgtttg tcacaggaat gccccactgg agtgttttct 120

ttcctcatct ctttatcttg atttagagaa aatggtaacg tgtacatccc ataactcttc 180

agtaaatcat taattagcta tagtaacttt ttcatttgaa gatttcggct gggcatggta 240

gctcatgcct gtaatcttag cactttggga ggctgaggcg ggcagatcac ctaagcccag 300

agttcaagac cagcctgggc aacatggcaa aacctcgtat ctacagaaaa tacaaaaatt 360

agccnggnat 370

<210> SEQ ID NO 65
<211> LENGTH: 316
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(316)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 65

gtcatggtgt tggcggggag tgtcttttag catgctaatg tattataatt agcgtatagt 60

gagcagtgag gataaccaga ggtcactctc ctcaccatct tggttttggt gggttttggc 120

cagcttcttt attgcaacca gttttatcag caagatcttt atgagctgta tcttgtgctg 180

acttcctatc tcatcccgna actaagagta cctaacctcc tgnaaattga agnccagnag 240

gtcttggcct tatttnaccc agcccctatt caaaatagag tngttcttgg nccaaacgcc 300

cctgacacaa ggattt 316

<210> SEQ ID NO 66
<211> LENGTH: 448
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

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<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(448)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 66

ctgcagnccg ggggatcctg gtaaaagtca caaggtcagc ctactaaagc agggaaaact 60

aaaggcaagt aaacacgtgc agacaaaaaa agggataaag aaaaggaatt aagaaactag 120

catttttaan gtgggggagg tgaatgcttc ccagaatggg tttatatcac ttgcttgngg 180

gccttctgag tgttggnaac aacctgtcat catcacacat acctgtcatc tttaatggtc 240

tccatacatt actaatagat tatacagatg gccatcactt aacacttcca ctcactcaat 300

ttgtncaaca tgcaaggtta ccctcttttt tngcttacng ccacaaagca ttgganaagg 360

tttgtgattt ttactagccn ccacttcatc aaatttaagc attttctttt tcctnttaac 420

anccaggaca ggnttnaacn aaggaaat 448

<210> SEQ ID NO 67
<211> LENGTH: 450
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(450)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 67

ctgcagctcc aagcaccttt ttcaaattca gctttctgtg atttcagacc acatatgcaa 60

ggaactatct taccttaatt aataagactt taaaatcctt gtgtcagagg cgtttggacc 120

agagcaactc tatcttgaat aggggctggg taaaataagg ccaagaccta ctgggctgca 180

tttgcaggag gttaggtact cttagttacg ggatgagata ggaagtcagc acaagataca 240

gctcataaag gatcttgctg ataaaactgg ttgcaataaa gaagctggnc aaaacccacc 300

aaaaccaaga tggtgaggag agtgacctct ggttatcctc actgntcact atacgntaat 360

tattatacat tagcatgcta aaagacactc cccgcaacaa ccatganagg tttacaagtt 420

nccatggnaa cgnncccgga ngntancttg 450

<210> SEQ ID NO 68
<211> LENGTH: 388
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(388)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 68

ctgnagcctc caccacccag gttcaggtga ttctcctgcc gtagnctcat gagtagntgg 60

gattacaggc atgtgccacc atgcccgact aatttttata tttttagtag agacggggtt 120

tcaccatgtt gggcaggctg gtctcaaact cctgacctca agtgatctgc ccaccttggc 180

ctcccaaagt gctgggattt caggcgcctg gcctgttact tgattatatg ctaaacaagg 240

ggtggattat tcatgagttt tctgggaaag aggtgggcaa ttcccggaac tgagggatcc 300

ctccccttnn nagaccatac aaggtaactt ccggacgttg gcatggnatc ttgttaaact 360

tgtcatggng ttgggggga gtgtcttt 388

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<210> SEQ ID NO 69
<211> LENGTH: 500
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(500)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 69

ctgcagaagt atgtttcctg tatggtatta ctggataggg ctgaagttat gctgaattga 60

acacataaat tcttttccac ctcagggnca ttgggcgccc attgctcttc tgcctagaat 120

attctttcct tttctaactt tggtggatta aattcctgtc atccccctcc tcttggtgtt 180

atatataaag tnttggtgcc gcaaaagaag tagcactcga atataaaatt ttccttttaa 240

ttctcagcaa ggnaagttac ttctatatag aagggtgcac ccntacagat ggaacaatgg 300

caagcgcaca tttgggacaa gggaggggaa agggttctta tccctgacac acgtggtccc 360

ngctgntgtg tnctnccccc actgantagg gttagactgg acaggcttaa actaattcca 420

attggntaat ttaaagagaa tnatggggtg aatgctttgg gaggagtcaa ggaagagnag 480

gtagnaggta acttgaatga 500

<210> SEQ ID NO 70
<211> LENGTH: 435
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(435)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 70

ctgcagagta attgcaactg gagttgtctt aagataatgt cacatatcca tcttcccctt 60

gtttctcatt cacagaaaaa cattttttatt ccaggtgcca atattcccag ccaaaaagac 120

tttacttctg actcccttat atttaggatg gctatgagaa caagtaaggg caatgacttc 180

tagggagatg tgttgtgtat ggaacttcta aggagagaat tctgctgaca tgtcctatgt 240

tcttttctcc cctactcctt cctactgtca gaaatgaagg ctagggctcc agcctggacc 300

ctgaagtaag ctagaggtta gaagctaaag aagaaagaag gagattgagt ccttggatga 360

acgtgaagcc accctactaa tctggactgn ctacctctgn actactctat gagagagaaa 420

gtatgtgcat tattt 435

<210> SEQ ID NO 71
<211> LENGTH: 439
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(439)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 71

catgctcttt gtccctgtga ctctctgcat ggtggtggtc gtggntacca ttaagtcagt 60

cagcttttat acccggaagg atgggcagct gtacgtatga gtttggtttt attattctca 120

aagccagtgt ggcttttctt tacagcatgt catcatcacc ttgaaggcct ctgcattgaa 180

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ggggcatgac ttagctggag agcccatcct ctgtgatggt caggagcagt tgagagagcg 240

aggggttatt acttcatgtt ttaagtggag aaaaggaaca ctgcagaagt atgtttcctg 300

tatggtatta ctggataggg ctgaagttat gctgaattga acacataaat tcttttccac 360

ctcaggggca ttgggcgccc attgntcttc tgcctagaat attctttcct ttnctnactt 420

gggnggatta aattcctgt 439

<210> SEQ ID NO 72
<211> LENGTH: 318
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(318)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 72

tccatctcta cgactctcat ggggtccaaa gaagagtttt aattgagttt tagaatgtgn 60

agttgtgaag tgtctgaaaa actacatggt gntctgaaag ncaaactttt agccttgggg 120

gagagcatct aagacagnag gtgaagggga ggggttagan ctagagggat tgaagaatat 180

tatccatata ggttagggtt aggtgtggca acgttttata gaacaaacat tggnaagcta 240

cagacacagg ccagntctgt ctnctacctn tccacaaagg tgtnataaca aagttannca 300

caaatgtgtg aataaact 318

<210> SEQ ID NO 73
<211> LENGTH: 450
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(450)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 73

gttgcaaagt catggattcc tttaggtagc tacattatca acctttttga gaataaaatg 60

aattgagagt gttacagtct aattctatat cacatgtaac ttttatttgg atatatcagt 120

aatagtgctt tttcnttttt ttttttttntt ttttttnnnt ttnggggana gagtctcgct 180

ctgtcgccag gttggagtgc aatggtgcga tcttggctca ctgaaagctc caccncccgg 240

gttcaagtga ttctcctgcc tcagccnccc aagtagntgg gactacaggg gtgcgccacc 300

acgcctggga taattttggg nttttttagta gagatggcgt ttcaccanct tggngcaggc 360

tggtcttgga actcctgana tcatgatctg cctgccttag cctccccaaa gtgctgggat 420

tncaggggtg agccactgtt cctgggcctc 450

<210> SEQ ID NO 74
<211> LENGTH: 489
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(489)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 74

ctgcagntga gccgtgattg canccacttt actccnagcc tgggcaanca aaatgagaca 60

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ctggctncaa acacaaaaac aaaaacaaaa aaagagtaaa ttaatttaaa gggaagtatt 120

aaataaataa tagcacagtt gatataggtt atggtaaaat tataaaggtg ggatattaat 180

atctaatgtt tgggagccat cacattattc taaataatgt tttggtggaa attattgtac 240

atcttttaaa atctgtgtaa tttttttttca gggaagtgtt taaaacctat aacgttgctg 300

tggactacat tactgttgca ctcctgatct ggaattttgg tgtggtggga atgatttcca 360

ttcactggaa aggtccactt cgactccagc aggcatatct cattatgatt agtgccctca 420

tggccctggt gtttatcaag taccncccctg aatggactgg gtggctcatc ttggctgtga 480

tttcagtat 489

<210> SEQ ID NO 75
<211> LENGTH: 449
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(449)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 75

ctgcagnctt gacctcctgg gatcaatcga tcctcccacc tcagcctcct aagtagctgg 60

aactacaggt gtgcaccacc atgcccggct aatttttgta ttttctgtag atacgaggtt 120

ttgccatgtt gcccaggctg gtcttgaact ctgggcttag gtgatctgcc cgcctcagcc 180

tcccaaagtg ctaagattac aggcatgagc taccatgccc agccgaaatc ttcaaatgaa 240

aaagttacta tagctaatta atgatttact gaagagttat gggatgtaca cgttaccatt 300

ttctctaaat caagataaag agatgaggaa agaaaacact ccagtggggc attcctgtga 360

caaacaaatt atcagtcttg ggttttacna tatactgaaa tcacagccaa gatgagccac 420

gcagtccatt cagggaggta cttgataaa 449

<210> SEQ ID NO 76
<211> LENGTH: 490
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(490)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 76

ttcttgccgt tcccgacccg agcctggtgc cccttcccca ttatgatcct tntcgcttcc 60

ggcggcatcg ggatgccccg cgttgcaggc catnctgtcc cagncaggta gatgacgacc 120

atcagggaca gcttcaagga tcgctcgcgg ctcttaccag cctaacttcg atcattggac 180

cgctgatcgt cacggcgatt tatcccgcct cggcgagcac atggaacggg ttggcatgga 240

ttgtaggcgc cgccctatac cttgtctgcc tcccccgcgt tgcgtcgcgg tgcatggagc 300

cggnccacct cgacctgaat ggaanccggc ggcacctcgc taacggattc accactccaa 360

gaattggagc caatcaattc ttgcggagaa ctgtgaatgc ncaaaccaac ccttggcaga 420

acatatccat cgcgtccgcc atctccanca gccgcacgcg gcgcatctcg ggcagcgttg 480

ggtcctgcag 490

<210> SEQ ID NO 77

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<211> LENGTH: 470
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(470)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 77

ctgcagtgtt taaaaaataa aataaactaa aagtttattt atgaggagta cactgctttc 60

ttgtaaacac atgtacaagc catataatag agttcatttc nnaccctagt tacggaaaca 120

ctagaaagtc tncacccggc caagataaca catctttagg taaaaatagc aagaaatatt 180

ttatgggttg tttacttaaa tcatagtttt caggttgggc acagtggntc atgcctgtaa 240

tcccagcact ttatgcggct gaggcaggca gatcagttga ggtcagaagt ttgagaccag 300

cctgggcaat gtggcaaaac ctcatctcca ctaaaaatac aaaaattagc caggcatggt 360

ggtgcacaca tgttaattcc cagctacttg ggaggnttga gacaggaggg tcgcttggnc 420

ctaggaggga agaagttgna gggancttaa tgtcactgca ctctagnttg 470

<210> SEQ ID NO 78
<211> LENGTH: 445
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(445)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 78

cactcaattc tgaatgctgc catcatgatc agtgtcattg ttgtcatgac tannctcctg 60

gtggttctgt ataaatacag gtgctataag gtgagcatga gacacagatc tttgntttcc 120

accctgttct tcttatggtt gggtattctt gtcacagtaa cttaactgat ctaggaaaga 180

aaaaatgttt tgtcttctag agataagtta atttttagtt ttcttcctcc tcactgtgga 240

acattcaaaa aatacaaaaa ggaagccagg tgcatgtgta atgccaggct cagaggctga 300

ggcaggagga tcgcttgggc ccaggagttc acaagcagct tgggcaacgt agcaagaccc 360

tgcctctatt aaagaaaaca aaaaacaaat attggaagta ttttatatgc atggaatcta 420

tatgtcatga aaaaattagt gtaaa 445

<210> SEQ ID NO 79
<211> LENGTH: 496
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(496)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 79

cctgtattta tactgaacca ccaggaggat agtcatgact acaatgacnc tgatcatgat 60

ggcagcattc agaattgagt gcagggctct ctggcccaca gtctcggtat cttctgtgaa 120

tggggtatag attctacaat aaaacaaaca caaaagccct aggtcagtgt taatggagat 180

caccaaccac attaccacct ccaacacaga attttctttt tcttaattca attcgnatct 240

tataagtcac ttttccccaa ctcaccaatn ctagctaaga atttttaacc tgagaaaaac 300

-continued

agctacactc taaaattgct tcaaagaaaa tgtctaacat atggaaagaa ggacttaaca 360

tgtgaagcag acactggctc catctagtgg gtgctttata ttgaaataat tataatacct 420

catcaaattt tttngggtac agnttattag gaacttggta tggaaccaga ttctgccaca 480

gaaaccacgn gggctg 496

<210> SEQ ID NO 80
<211> LENGTH: 496
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(496)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 80

cattagataa tggntcaggg tggccaaggc tccgtctgtc gttgtgctcc tgccgttctc 60

tattgtcatt ctataagcac aagaaaaaca ttttcagtaa atcagattct cagcagaatc 120

aaggtaacgg ttagacctgg gattaacaac agacccgtca ctatgagttc taaaaacctg 180

aagcaagaaa aaacaatgta caggaagtat gcagtttaaa agtctagatt atctatcatt 240

gttcactgaa ggcattcagg tcctctcttt tacctgggtc ttggnttgct ccattctctc 300

tgttcatccc aacatacaca attgtactta tcctttgaga tgtaccttaa atactgacac 360

ctgcatgaaa acttgtttac tggctgcagg tccaagcacc tttttcnaaa ttcagctttc 420

tgtgatttca gaccacatat gcaaggaact atcttacctt aattaataag antttaaaat 480

ccttgtgtca gaggcg 496

<210> SEQ ID NO 81
<211> LENGTH: 368
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(368)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 81

aggancgctt gggcccagga gttcacaagc agcttgggca acgtagcaag accctgcctc 60

tattaaagaa aacaaaaaac aaatattgga agtattttat atgcatggaa tctatatgtc 120

atgaaaaaat tagtgtaaaa tatatatatt atgattagnt atcaagattt agtgataatt 180

tatgttatnn ngggatttca atgccttttt aggccattgt ctcaaaaaat aaaagcagaa 240

aacaaaaaaa gttgtaactg aaaaataaac atttccatat aatagcacaa tctaagtggg 300

tttttgnttg tttgtttgnt tgttgaagca gggccttgcc ctnccaccca ggntggagtg 360

aagtgcag 368

<210> SEQ ID NO 82
<211> LENGTH: 500
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(500)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 82

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gaattccttt ttttttttt ttttttttt ttnctcctaa tgtttttatt gtnccttaga 60

taactggata gnacaaagtt ngncttngtt ttttacttaa aaaacgtact ttccgcatac 120

tgtngcccgt atgactttcc tgtcccatcg gaaaccagag tttccccagg tgagcccttc 180

ctatctgngg ntacatgatt tagctaattt aacaagaaga gagtaattcc ttnggattat 240

tatcaacatg aaacttggac tatgtctcta taagggtgaa cactgatttt ttttttcttt 300

ttagaaacaa aaaccatcca cttattaatc caaactacgg gattggattt acaacaatca 360

tcgcatnaac tgaacatacg aagttaccac tcaagggaat nacagaagaa cgttgnacaa 420

tntntcttac ggggtacgng aattcaaaca atgtggggan aggaacttca ntctacaaan 480

tctgaccatc gnttcagtat 500

<210> SEQ ID NO 83
<211> LENGTH: 450
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(450)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 83

gaattccttt actcttcttt aattctaccg tctttgggca tacatctcat ttgntgtgga 60

agaaggtctg acagnagggc tgacagcacc gattcataac acattctttt catcatacaa 120

agagtaagac cctagaataa tgggaccatc tgctaccacg acagagctgc cttactggct 180

gtagaaaaag actgcttgtg tgggagagaa gaatgaggac agaggaggca tctggggcaa 240

gtgagcgtac aagtatntct acaaattcag aatttggtgg aaaatccaaa tttgncttca 300

acatgataga gaattgatga gaaaatagct gtnctgtttc caaaatttac tgaatttggg 360

aacctgaggt taaaactttt aggatnaagc aactcaggtt caagacttng nctngggaag 420

gaatggaaac acagacggga atgagtntca 450

<210> SEQ ID NO 84
<211> LENGTH: 450
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(450)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 84

caactgtatt tatacagnaa ccaccaggag gatagtcatg acaacaatga caaactagga 60

atagcccccc ttcacttctg agtcccagag gttacccaag gcacccctct gacatccggc 120

ctgcttcttc tcacatgana aaaactagcc cccagtntga tccgcaggtn gaggaatncc 180

ccgggtcgag gttcggatcc tggatgacag accctctcgc ccctgaaggn gataaccggg 240

tgtggtacat ggacggntat cacaacaacc gcttcgnacg tgagtacaag tccatggttg 300

acttcatgaa cacggacaat ttcacctccc accgtctccc ccacccctgg tcgggcacgg 360

ggnaggtggt ctncaacggt tctttctnct tcaacaagtt ccagagccac atcatcatca 420

ggtttggacc tgaaganaga gaacatcctc 450

<210> SEQ ID NO 85
<211> LENGTH: 500

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<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(500)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 85

ggatccctcc ccttttaga ccatacaagg taacttccgg acgttgccat ggcatctgta 60

aactgtcatg gtgttggcgg ggagtgtctt ttagcatgct aatgtattat aattagcgta 120

tagtgagcag tgaggataac cagaggtcac tctcctcacc atcttggttt tggtgggttt 180

tggccagctt ctttattgca accagtttta tcagcaagat ctttatgagc tgtatcttgt 240

gctgacttcc tatctcatcc cgtaactaag agtacctaac ctcctgcaaa tngcagccca 300

gtaggtcttg gncttatttt acccagcccc tattcaagat agagttgctc ntggtccaaa 360

cgcctctgac acaaggattt taaagtctta ttaattaagg taagataggt ccttggatat 420

gtggtctgaa atcacagaaa gctgaatttg gaaaaaggtg cttggagctg cagccagtaa 480

acaagttttc atgcaggtgt 500

<210> SEQ ID NO 86
<211> LENGTH: 500
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(500)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 86

ctgcagtgag ccaaaatcgt gccactgcac ttcactccag cctgggtgac agggcaaggc 60

cctgcttcaa caaacaaaca aacaaacaaa aacccactta gattgtgcta ttatatggaa 120

atgtttattt ttcagttaca actttttttg ttttctgctt ttatttgttg agacaatggc 180

ctaaaaaggc attgaaatnc caaaataaca taaattatca ctaaatcttg ataactaatc 240

ataatatata tattttacac taatttttttc atgacatata gattccatgc atataaaata 300

cttccaatat ttgtttttttg ttttctttaa tagaggcagg gtcttgctac gttgcccaag 360

ctgcttgtga actcctgggc ccaagcgatc ctcctgcctc agcctctgag cctggcatta 420

cacatgcacc tggcttcctt tttgtntttt ttgaatgttc cacagtgagg aggaagaaaa 480

ctnaaaatta acttatctct 500

<210> SEQ ID NO 87
<211> LENGTH: 450
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(450)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 87

ctgcagatga gaggcactaa ttataagcca tattaccttt cttctgacaa ccacttgtca 60

gcccacgtgg tttctgtggc agaatctggt tctataacaa gttcctaata agctgtagcc 120

aaaaaaattt gatgaggtat tataattatt tcaatataaa gcacccacta gatggagcca 180

gtgtctgctt cacatgttaa gtccttcttt ccatatgtta gacattttct ttgaagcaat 240

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tttagagtgt agctgttttt ctcaggttaa aaattcttag ctaggattgg tgagttgggg 300

aaaagtgact tataagatac gaattgaatt aagaaaaaga aaattctgtg ttggaggtgg 360

taatgtgggt ggtgatcttc attaacactg anctagggnt ttggggtttg gtttattgta 420

gaatctatac cccattcana gaagataccg 450

<210> SEQ ID NO 88
<211> LENGTH: 502
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(502)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 88

ctgcagccag taaacaagtt ttcatgcagg tgtcagtatt taaggtacat ctcaaaggat 60

aagtacaatt gtgtatgttg ggatgaacag agagaatgga gcaagccaag acccaggtaa 120

aagagaggac ctgaatgcct tcagtgaaca atgatagata atctagactt ttaaactgca 180

tacttcctgt acattgtttt ttcttgcttc aggtttttag aactcatagt gacgggtctg 240

ttgttaatcc caggtctaac cgttaccttg attctgctga gaatctgatt tactgaaaat 300

gtttttcttg tgcttataga atgacaatag agaacggcag gagcacaacg acagacggag 360

ccttggccac cctgagccat tatctaatgg acgacccagg gtaactcccg gcaggtggtg 420

gagcaagatg aggaagaaga tgaggagctg acattgaaat atggcggcna gcatgtgatc 480

atgctcnttg gccctgtgan tc 502

<210> SEQ ID NO 89
<211> LENGTH: 499
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(499)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 89

ctgcagtgtt ccttttctcc acttaaaaca tgaagtaata acccctcgnt ctctcaactg 60

ctcctgacca tcacagagga tgggctctcc agctaagtca tgccccttca atgnagaggc 120

cttcaaggtg atgatgacat gctgtaaaga aaagccacac tgggtttgag aataataaaa 180

caaaactcat acgtacagct gcccatcctt ccgggtataa aagctgactg acttaatggt 240

agccacgacc accaccatgc agagagtcac agggacaaag agcatgatca catgcttggc 300

gncatatttc aatgtcagnt cctcatcttc ttcctcatct tgntccacca cctgccggga 360

gttaccntgg gtcgtccatt agataatggg tcagggtggc caaggctccg tctgtcgttg 420

tgctcctgcc gttctctatt gtcattctat aagcacaaga aaaacatttn cagtaaatca 480

gatnctcagc agaatcaag 499

<210> SEQ ID NO 90
<211> LENGTH: 500
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(500)

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<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 90

taactcccag gntcaagatn tctncctgcg ttagcctcct gagtagctgg gactataggt 60

atgtgccact attcctgaaa acataatcag ttttgaaggt agtgtctggg ctgggcgcag 120

tggntcacgc cttcaatccc agcactttgg gaggncgagg tgggcggatc acctgaggtc 180

aggagttcga gaccagcctg accaacatgg gataagactc catctctact aaaaatacaa 240

aaaattagcc aggcatggtg gngcatgcct gtaatcccag ctactcagga ggntgaggna 300

ggagaattgg ttggaaccta ggaagcagag gctgtggtgg agccgagatc gcaccattgg 360

actccaggct gggnaacaag agtgaaaatc cntcttaaaa aaaaaaaaaa aaaggtagng 420

ttttgnccgg ngcgggggggt cacgcctgta atcccagnat tggggganggc aaggnggggg 480

gtcannangn nagnagtccg 500

<210> SEQ ID NO 91
<211> LENGTH: 502
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(502)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 91

gaattctgct gacatgtcct atgttctttt ctcccctact ccttcctact gtcagnaatg 60

aagggtaggg ctccagcctg gaccctgaag taagctagag gttagaagct aaagaagaaa 120

gaaggagatt gagtccttng atgaacgtga agccaccgta ctaatctgga ctgcctacct 180

ctgcactact ctatgagaga gaaagtatgt gcattattta aaccagttgg gttgattttc 240

tattaacaaa gtcagaaaca tctctgtaaa aagccagact gaatatttta agctctatgg 300

gtcatatggt ctccagggca aacactcaac tgtgctactg tagtgtgaaa gcaggcacag 360

acaatgtatt aaccaaggag ggtggtcact ttccaatgaa agtttatcac aaattggnga 420

atacttggta ttacaccnng ggggaaggta ggagaagatc ttgcctgtgg ttgtngntgg 480

caatgttggt cttttatacg ng 502

<210> SEQ ID NO 92
<211> LENGTH: 495
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(495)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 92

gaattctctc cttagaagtt ccatacacaa cacatctccc tagaagtcat tgcccttact 60

tgttctcata gccatcctaa atataaggga gtcagaagta aagtctggnt ggctgggaat 120

attggcacct ggaataaaaa tgtttttctg tgaatgagaa acaaggggaa gatggatatg 180

tgacattatc ttaagacaac tccagttgca attactctgc agatgagagg cactaattat 240

aagccatatt acctttcttc tgacaaccac ttgtcagccc acgtggtttc tgtggcagaa 300

tctggttcta taacaagttc ctaataagct gtagccaaaa aaatttgatg aggtattata 360

-continued

attatttcaa tataaagcac ccactagatg gagccagtgt ctgcttcaca tgttaagtcc 420

ttctttccat atgttagaca tttctttgaa gcaattttag agtgtagctg tttctcaggt 480

taaaattctt agtag 495

<210> SEQ ID NO 93
<211> LENGTH: 500
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(500)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 93

tatggttgcc tattcttgtc acagtaactn aactgatcta ggaaagaaaa aatgttttgt 60

cttctagaga taagttaatt tttagttttc ttcctcctca ctgtggaaca ttcaaaaaat 120

acaaaaagga agccaggtgc atgtgtaatg ccaggctcag aggctgaggc aggaggatcg 180

cttgggccca ggagttcaca agcagcttgg gcaacgtagc aagaccctgc ctctattaaa 240

gaaaacaaaa aacaaatatt ggaagtattt tatatgcatg gaatctatat gtcatgaaaa 300

aattagtgta aaatatatat attatgatta gttatcaaga tttagtgata atttatgtta 360

ttttgggatt tcaatgcctt tttaggccat tgtctcaaaa aaataaaagc aggaaaacaa 420

aaaaagttgt aacttgaaaa ataaacattt ccatatttat agccaactaa gtgggtttng 480

ggtnggttgg gttggttggt 500

<210> SEQ ID NO 94
<211> LENGTH: 385
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(385)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 94

ttatcattaa caggtcccac aacccttaaa aagtacagat ttttttttc ttngtggaga 60

cagggtctca cttggtcgcc cagactggag tgcagtggca cgatctcagt tcaccacaac 120

ctctgcctcc tgggttcaag caatnctcgt gcttaagcct cctgagtagg tggaaccacg 180

cgtgcgcgcc accacgctag gttnattgtg gctttttag tagagacagg gtttcgccat 240

gttgcccagg ctggtctcan attccngacc tcaagtgatc cgnccgcctc agactcccaa 300

agtgntgagc attacagntg tgtaccacta tgtcccngnc cncatctctc tttaaaacan 360

cttncattta cctagtccac tcctg 385

<210> SEQ ID NO 95
<211> LENGTH: 330
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(330)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 95

gacctagaaa agaaagcatt tcaannntaat taacaggtcc cacaaccctt aaaaagtaca 60

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gatttttttt ttctttnngg agacagggtc tcactttgtc gcccagactg gagtgcagtg 120

gcacgatctc agctcaccac ancctctgcc tcctgggttc aagnanttct cgtgcttang 180

cctcctgagt aggtggaacc acgcgtgtgc gccaccacgc taggctactt tntgtatttt 240

tagtagagac agggtttcgc catnttgccc aggctgntct caaattcctg acccncaagt 300

gatccccccn ccttcagtac tccccatcag 330

<210> SEQ ID NO 96
<211> LENGTH: 382
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(382)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 96

ggtggncgtt ctagaactag tggcncccaa ggnagaagaa gttttcttag tacagaacaa 60

aatgaaangt ctcccatgtc tacttctttc tacacagaca cggcatccat ccgtttttct 120

cantctttcc nccacctttc ccgtctttct attccacaaa gccgncattg tcatcctggc 180

ccnttctcaa tgagctgttg nntacacctc ccagacggcg tggtggncgg tcagaggggc 240

tcctcacttc ccagtagggg tggccgngca ggnggtgccc cncacccccc gggcggggtg 300

gttngtccnn ccggngggnt gcaccncccc caccctccc cnctctncta ctggcggtcg 360

tntattncan natctttaag ca 382

<210> SEQ ID NO 97
<211> LENGTH: 360
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(360)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 97

ggatccaaag gaagttagag gccagctcag tctacacctg ctactgntca gtgcccaccc 60

ggtcaaggga gaccaacaca tggtaaaggt caagggcttc ttggaaggca gtcagcagcc 120

tgtgcaagat gttctccaca ctgctcagnt taaggggagc tgggggcagg acctcagctg 180

gnatctctgc ttcaccagtg tccaggggtt gcacaattct tgtttactcg taggatattt 240

aatcttggnn ggtgctatca taaatgggac ttatccnctn attatgtttt cttactagtt 300

gtttatgtga aggttattga tttgggtttc actttatttn gtggnaatgg agtttcactc 360

<210> SEQ ID NO 98
<211> LENGTH: 208
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(208)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 98

aatgtcacgg attcctttag gtagntacac ccatcaacct ttttgagaat aaaatgaatt 60

gagagtgtta cagtctaatt ctatatcaca tgtaactttt atttggatat atcagtaata 120

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gtgctttttt ttttttttt ttttttttt ttttttttng gnganagagt ctcgctctgt 180

cgccaggttg gagtgnaatg gtgcgatc 208

<210> SEQ ID NO 99
<211> LENGTH: 470
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(470)
223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 99

aacaaggttt ctcggtcggc ggtgaatata ccggggcgtc gatatttgtt gcggaatact 60

cccctgaccg taaacgtggc tttatgggca gctggctgga cttcggttct attgccgggt 120

ttgtgctggg tgcgggcgtg gtggtgttaa tttcgaccat tgtcggcgaa gcgaacttcc 180

tcgattgggg ctggcgtatt ccgttcttta tcgctctgcc gttagggatt atcgggcttt 240

acctgcgcca tgcgctggaa gagactccgg cgttccagca gnatgtcgat aaactggaac 300

agggcgaccg tgaaggtttg gaggatggcc cgaaagtctc gtttaaagag attggcacta 360

aatactggng cagnctgttg aatgtttggg cttggtaatt ggcaaccaac gtgattacta 420

natgttggtg acctatattg ccgagttatt ggcggataac ctgaattatc 470

<210> SEQ ID NO 100
<211> LENGTH: 440
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(440)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 100

taattatatt gaaatgcttc tcntctaggt catccatgnc tggnttatta tatcatctct 60

attgntgntg ctctttttta catncattta cttggggtaa gttgtgaaat ttggggtctg 120

tctttcagaa ttaactacct nngtgctgtg tagctatcat ttaaagccat gtactttgnt 180

gatgaattac tctgaagttt taattgtntc cacatatagg tcatacttgg tatataaaag 240

actagncagt attactaatt gagacattct tctgtngctc ctngcttata ataagtagaa 300

ctgaaagnaa cttaagacta cagttaattc taagcctttg gggaaggatt atatagcctt 360

ctagtaggaa gtcttgtgcn atcagaatgt ttntaaagaa agggtntcaa ggaatngtat 420

aaanaccaaa aataattgat 440

<210> SEQ ID NO 101
<211> LENGTH: 449
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(449)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 101

aaaacaaagc ctcttgaggt tctgaaaagg gaaagaaaaa cagaactttg tgcactacaa 60

ttatactgtt ataaaaaaca cttccataga ttacattaag cagaaacaaa cctttctttc 120

-continued

atgtgttctc ctccaggcca agctgtctaa ggaccgcaaa ggctgttgtc acttgcaggc 180

tcccagatta ggtctgaaat aggatttcac caggtcatcc attgttagtt aaatcctagt 240

aaattcattt anaccaatca aatacttata agaccaattt gtaaaccagg aatgtattaa 300

tttgtcacga ctttcaacta actgacaaat ttactataag ctcaaggtag gactctttag 360

caataagtag gaaccgcctg agacaaccaa acattttcaa cccacaaang atactttaat 420

gactttctga tttnccagca aaaggggggg 449

<210> SEQ ID NO 102
<211> LENGTH: 425
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(425)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 102

ggatccgccc tcctcggcct cccaaagtgt tgggattaca ggcgtgagcc accgcacctg 60

gctttttttt ttttttttt tggnggagac agagtcttac tctgttgccc aagctggagt 120

gcagtggtgc aatcttggtt cactgnaacc tccacctcca gagttcaagc aattctctgc 180

ctcagtttct ggagtagctg ggattacagg tgcctgccat cacgcctggc taaatttggn 240

attttttttt agtagagaca gggtttcacc atgttggcca ggctggtctt gaactcctga 300

ccttgtgatc caccagcctc ggcctcccaa attgntggga ttacaggcgt gagccaccac 360

aaccaggcta aagttttaaa acatgccaag tgtatttaca taatgcgata cganttatgt 420

acata 425

<210> SEQ ID NO 103
<211> LENGTH: 386
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(386)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 103

ggatccgccc gccttggcct cccaaagtgc tgggattaca ggcatgagcc accgctcctg 60

gctgagtctg cgatttcttg ccagctctac ccagttgtgt catcttaagc aagtcactga 120

acttctctgg attcccttct cctnttgtaa aataagcatg ttatctgtcc nncctgcctt 180

gggcattgtg ataaggataa gatgacatta tagaatntng caaaattaaa agcgctagac 240

aaatgatttt atgaaaatat aaagattagn ttgagtttgg gccagcatag aaaaaggaat 300

gttgagaaca ttccnttaag gattactcaa gctccctttg gtgtatatca gnngtcanna 360

cntatcttng gggctgaaaa atgttt 386

<210> SEQ ID NO 104
<211> LENGTH: 224
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(224)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

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<400> SEQUENCE: 104

gaaaagggaa agaaaaacag aactttgtgc actacaatta tactgttata aaaaacactt 60

ccatagatta cattaagcag aaacaaacct ttctttcatg tgttctcctc caggccaagc 120

tgtctaagga ccgcaaaggc tgttgtcact tgcaggctcc cagattaggt ctgaaatagg 180

atttcaccag gtcatccatt gttagttaaa tcctagtaaa tnca 224

<210> SEQ ID NO 105
<211> LENGTH: 440
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(440)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 105

ggatccgccc tcctcggcct cccaaagtgt tgggattaca ggcgtgagcc accgcacctg 60

gctttttttt ttttttttt tggnggagac agagtcttac tctgttgccc aagctggagt 120

gcagtggtgc aatcttggtt cactgcaacc tccacctcca gagttcaagc aattctctgc 180

ctcagtttct ggagtagctg ggattacagg tgcctgccat cacgcctggn taaatttggg 240

attttttttt agtagagaca gggtttcanc atgttggcca ggntggtctt ggactcctga 300

cctggtgaac caccaggctc gggctccaaa tttggttggg attacagggg gtnaancaac 360

cacaacccag nctaaagttt tnaaaacatn caaagtgttt taaaatnatg ngatacgatt 420

tattgtacaa ttaattttat 440

<210> SEQ ID NO 106
<211> LENGTH: 448
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(448)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 106

gtctttccca tcttctccac agagtttgtg ccttacatta ttactccttg ccattttcaa 60

gaaagcattg tcagctcttc caatctccat caccttgggg cttgttttct actttgccac 120

agattatctt gtacagcctt ttatggacca attagcattc catcaatttt atatctagca 180

tatttgcggn tagaatccca tggatgtttc ttctttgact ataacaaaat ctggggagga 240

caaaggtgat tttcctgtgt ccacatctaa caaagtcaag atccccggct ggacttttgg 300

aggttccttc caagtcttcc tgaccacctt gcactattgg actttggnaa ggaggtgcct 360

atagaaaacg attttggaac atacttcatc gcaggggggac tgtgtccccc ggtggcagaa 420

nctaccaaga tttgcgggnc gaggtcaa 448

<210> SEQ ID NO 107
<211> LENGTH: 198
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(198)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

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<400> SEQUENCE: 107

ggatccgccc gccttggcct cccaaagtgc tgggattaca ggcatgagcc accgctcctg 60

gctgagtctg cgatttcttg ccagctctac ccagttgtgt catcttaagc aagtcactga 120

acttctctgg attcccttct ccttnagtaa aataagnatg ttatctgncc gccctgcctn 180

ggnnattgng ataaggat 198

<210> SEQ ID NO 108
<211> LENGTH: 500
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(500)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 108

ctgcagtgag ccgtgattgc accactttac tccagcctgg gcaacaaaat gagaccctgg 60

ctcaaaaaca aaaacaaaaa caaaaaaaga gtaaattaat ttaaagggaa gtattaaata 120

aataatagca cagttgatat aggttatggt aaaattataa aggtgggata ttaatatcta 180

atgtttggga gccatcacat tattctaaat aatgtnttgg tgaaaattat tgtacatctt 240

ttaaaatctg tgtaattttt tttcagggaa gtgtttaaaa cctataacgt tgctgtggac 300

tacattactg ttgcactcct gatctggaat tttgggtgtg gtgggaatga tttccattca 360

ctggaaaggt ccacttcgac tccagcaggc atatctcatt atgattagtg cctcatggnc 420

ctggtgttta tcaaagtacc tccctgaatg gactgcgtgg gtcatcttgg ntgtgattca 480

gtatatggta aaacccaaga 500

<210> SEQ ID NO 109
<211> LENGTH: 500
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(500)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 109

ctgcagcctt gacctcctgg gatcaatcga tcctcccacc tcagcctcct aagtagctgg 60

aactacaggt gtgcaccacc atgcccggct aatngntgta ttttctgtag atacgaggtn 120

tngccatgtt gcccaggctg gtcttgaact ctgggcttag gtgatctgcc cgcctcagcc 180

tcccaaagtg ctaagattac aggcatgagc taccatgccc agccgaaatc ttcaaatgaa 240

aaagttacta tagctaatta atgatttact gaagagttat gggatgtaca cgttaccatt 300

ttctctaaat caagataaag agatgaggaa agaaaacact ccagtggggc attcctgtna 360

caaaacaaat tatcagtctt ggggtttnac catatactga aatcacaggc aagatgagcc 420

acgcagtcca tncagggagg tactggataa caccagggnc atgagggact aatcataatg 480

agatatgctg ctggagtcga 500

<210> SEQ ID NO 110
<211> LENGTH: 550
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature

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<222> LOCATION: (1)..(550)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 110

ctgcaggatg agagcgatct cttnttncat ttcctgcgct acgcgctgcg ggcgaccaaa 60

ttctttcgcc ataataaatt ctcctgacna aaaaggggct gttagcccct ttttaaaatt 120

aatttcaggt ggaagggctg ttcacgttga cctgataaga cgcgccagcg tcacatcagg 180

caatccatgc cggatgcagc gtaaacgcct tatcccgcat ggaaccctaa aaaccttaag 240

caatggtacg ttggatctcg atgatttcga atacttcgat cacatcgnca gtgcggacgt 300

cgttgtagtt cttaacgccg ataccacatt ccataccgtt acgggacttc gttaacgtca 360

tctttggaag cggggcaggg actccagctc gncttcgtag ataaccacgt tggcacgcag 420

gaacgcgggt cgggttgtga cgtttaacac aacttccggg taaccataca ggctgngatg 480

gnaccaaatt tcgggggatt tggacaagtc aagaacttcc cgccagaccg ataatcttgt 540

tgttcagttc 550

<210> SEQ ID NO 111
<211> LENGTH: 541
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(541)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 111

ctgcagcttt cctttaaact aggaagactt gttcctatac cccagtaacg atacactgta 60

cactaagcaa atagcagtca aacccaaatg aaatttntac agatgttctg tgtcatttta 120

tnttgtttat gttgtctccc ccacccccac cagttcacct gccatttatt tcatattcat 180

tcaacgtctn nntgtgtaaa aagagacaaa aaacattaaa ctttttttcct tcgttaattc 240

ctccctacca cccatttaca agtttagccc atacatttta ttagatgtct tttatgtttt 300

tcttttncta gatttagtgg ctgngttgtg tccgaaaggt ccacttcgta ttgctggttg 360

aaacagctca ggagagaaat gaaacgcttt ttccagctct catttactcc tgtaagtatt 420

tggagaatga tattgaatta gtaatcagng tagaatttat cgggaacttg aaganatgtn 480

actatggcaa tttcanggna cttgtctcat cttaaatgan agnatccctg gactcctgna 540

g 541

<210> SEQ ID NO 112
<211> LENGTH: 241
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(241)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 112

nncccncncn nnnnnnnttn ntnttgcccg ataactatag ggngacttgg agatccaccg 60

cggtggcggn cgntctagaa ctagtggatc ccccgggntg caggacccaa cgctgcccga 120

gatgcgccgc gtgcggttgc tggagatggc ggacgcgatg gatatgttct gccaagggtt 180

ggtttgcgca ttcacagttc tccgcaagaa ttgattggct ccaattcttg gagtggtgaa 240

-continued

t 241

<210> SEQ ID NO 113
<211> LENGTH: 834
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(834)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 113

ccccccncc nnnnnttttn ngcagcccgt aattaccctc actnccggga acaaaagctg 60

ggtaccgggc ccccctcga ggtcgacggt atcgataagc ttgatatcga attcctgcag 120

tgtttaaaaa ataaaataaa ctaaaagttt atttatgagg agtacactgc tttcttgtaa 180

acacatgtac aagccatata atagagttca ttttttaccc tagttacgga aacactagaa 240

agtcttcacc cggccaagat aacacatctt tagtaaaaat agcaagaaat attttatggg 300

ttgtttactt aaatcatagt tttcaggttg ggcacagtgg ntcatgcctg taatcccagc 360

actttatgcg gntgaggcag gcagatcagt tgaggtcaga agtttggaga ccagnctggg 420

caatgtggna aaacctcatc tccactaaaa atacaaaaat tagncaggca tggtggtgca 480

cacatgtaat tccagntact tggggaggct gagacaggag gatcgnttga acctagggag 540

ggaggagttg gagtgagcta atgtcaatgc actcttggtt ggggcganag agcaagatct 600

ttcttccaaa aaaaaaaaaa aaaaaaaagc caggtgnggn ggtcaaggct gtaatccaga 660

attngggagg ccgnggaggn natcantgng gnaggngtca agnggggcng gccacatggg 720

gaacccgttn ttnttaaatn aaaattagcc ggggngggggg aggactntat ccngttccgg 780

nggtgnggag gatcnttatt ntggnggagg gtggatgnnc cagttgacnc cccc 834

<210> SEQ ID NO 114
<211> LENGTH: 838
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(838)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 114

ttgggcncnc gccccttaan ttttttatngn ttnctanaaa aanannnggc ncnntaaaat 60

atatttttttn ttgtgacccc ttttaaaagg gacccnctaa aaaattttnt ggttnntttn 120

gatttangtg ggtgnttttn ttatattttt ggngagnntc tgtagtcntc nccctcaaac 180

anntcntacn atnggnancg tgactctgtc nttngtnann ntcgntntcn ngtnattcna 240

ggnncctcgc gcnncncggg cnnngttttt tttnncnntt tttaagccna annctcagta 300

ncntccaacg gngctnngac annngnnnct ntcgngggtn ccctctntnt ngnncnnggc 360

tnnngnnnnc ngncngcngn gccntgcgnn nngnnngngg nnngntnnca tanggatngn 420

gntgctcnnc ncnngngtnn tnagtaggna nttttntnnt acttgccnnc nnntngctgc 480

gagnanagcn anntngnngn agngnngntg cgcggannтt cccctgatna nctcgagcng 540

nttacnggng cnncctngaa naagngnngt anngtgccga gncgctannc tgagcctgag 600

tntcgacngg natngtgnnt cntacngtta ngggnngcnn gancgggntg antcnccggn 660

-continued

ngancnagcg actgcctntc angcgaancg tntcangnnn gtagagcana gggtnannng 720

tcnnnnaagc ntnnagtgan tgtcntnacn ngtganttac ggcntagnct tgatntnnan 780

ncgaggnnnn atnnannntt ggananttnn tnnnntcncn tcgcggngng ncnngccg 838

<210> SEQ ID NO 115
<211> LENGTH: 803
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(803)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 115

attcgcgcgt agcccgataa ctatagggcg acntggagnt ccaccgcggt ggcggccgct 60

ctagnaacta gtggatcccc cgggctgcag gaattcacgg actaatcctc tacagatctt 120

gctggagtgg cctttcagcc ttttgtgact gtttgtagtg aaatgtacac acaagcctac 180

aaggcagccc agatgtacca taactgtggg aaaattaaaa aaaaaaaaac acagaacctc 240

tctatgttgc ccatgctgga ctcaaactct tagacaagca atcctcgtac ctcagcctcc 300

tgagttcctg agtagctggg actacaagca tgcaccacca tgccaggcta tgagaaagtt 360

ctttttattg atccagacct tattgcctgg taacttccac cactgttcct agctctgntc 420

tctggtccta acagaggaaa atcttgaccc cacacctagt gcaactggat agcttatngt 480

tgggctngtg tttcctctat tctgggtcca ccctaaaatc cnatagatac tccaactgct 540

canagnaaac caagctctct ctctnncttn ctttcttnnn ctctattnat tnatgggnna 600

tnattnattn nggggatggn gttcggtcgc cgcccggctg gngtgaaatg ggggaggcaa 660

tcaatttaac cccacccngg gtccagggat ctcgttnaaa ccgnnnnnnn nnnnnnnnna 720

ngnncnncnc nnnccnntnn nnnggtttnn nngnnnnggg nnnccnnnnn nannnnnntn 780

nnnccnccna nnntncnnnn ccc 803

<210> SEQ ID NO 116
<211> LENGTH: 780
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(780)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 116

cnnnnnnncc cnntnattnt acgccagccg cgtaattaac cctcactaaa gggaacaaaa 60

gctgggtacc gggcccccc tcgaggtcga cggtatcgat aagcttgata tcgaattcca 120

actcctcact tgccagatgt gaccttaagc aagtgaactt ctgtgtgcca cactgttttc 180

atctgtaaaa ggataaaggg aatatcataa attagnttgt taagccttag tttaataatg 240

tctctaagtt ttacatataa gtagacagtg tctttcttgt ttagtgaata atcattctta 300

ttatttaata gtatctctac taaatttatt gtgtaagatt atactaatct tgtttagtgc 360

gtggtaatca cttctgctca tatttaacct ataagcataa tatagtttat ttatatacca 420

nttatttatt ttatttttatt tgnngagatg cagcttgtct tttncaaccc agggntgngg 480

ngnagnngng naancttgnt tcactgnaac cnccaccncc caggtncaag ngattctcct 540

gntcaagccn cctnagnagn tggnattaca gnacgantac annccagnta nnnnggntnt 600

-continued

nngntngnna ggnnncacan nngncaggtn nntcgnctcc nngccantna ctnnnnccan 660

ccccnnngnn nnnnatanag natnancann nnccncnnnn ncnnnnnnng gnggannccn 720

nntngcngnn anngnnannn nntnnnnnnn nnggncnnng nnnnnnnncc nnnnnncccc 780

<210> SEQ ID NO 117
<211> LENGTH: 803
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(803)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 117

nnnnnnnnnc cnnnnnnttc gnncgtaacn cgantcacta tagggcgact tggagctcca 60

ccgcggtggc ggccgctcta gaactagtgg atcccccggg ctgcaggaat tcgatatcaa 120

gctttngtgt gtaaaaagta ttagaatctc atgtttttga acaaggttgg cagtgggttg 180

ggaggaggga ttggagattg atgcgatagg aatgtgaagg gatagcttgg ggtggatttt 240

atttttaat tttaattttt atttnttgag atggagtctt gctctgtctc ccaggctgga 300

gtgcagtggt gtgatctcag ctcacgggtt caagcgattc tcctgctgca gcctcccgag 360

tagctgggat tacaggagcg cgccaccaca cccggntaat ttnnttgtat ttttagtaga 420

gacggggttt caccatgttg gttaggctgg tctagaactc ccaacctcat gatccgcctg 480

cttcggcctc ccaaagtgcc ggaattacag gcgtgagcga ctgcacccgg ccgcttgggg 540

gtggattttt aaagaaattt agaagaatgt aacttggcca gataccatgt acccgttaat 600

tcatttncgg ttttttggat acccattttg nnattctccc nccactggat aaataagggn 660

ggttcattnt ngnttagttt gggtnttttt nagtgtggnt tctgcttatn attagaatgg 720

nctnctttnc caanctggaa agggaggagt taaaatcant accagaanca gaaattcttt 780

tcanttgttg cncnagaaat gcc 803

<210> SEQ ID NO 118
<211> LENGTH: 819
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(819)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 118

tnccnnnncn nnnnnaattt tngcagncgc gtaattaacc tcactaaagg gaacaaaagc 60

tgggtaccgg gccccccctc gaggtcgacg gtatcgataa gcttccctcc ccttcctcag 120

ctctggcgac cctgcgctgt ggtggttctc caaccacact cattctcctc agctggctcc 180

ttgctcttct tccacccccc cgttggaagt gttcctaagt gtttggcttg gcctcctctt 240

ccccttcctt agnttagact tctccactgc tccaacatca actggaaatc tatggaattg 300

attcctgttt tcagctccag tcctgttcac agggcatttt cacctgctgg cacttccaaa 360

gtgacacttc caaaccactt cctcgccctc ctctctaaac caggtctttc ttcctaactt 420

ccttatttct gagaatgtct ctgncatgtt ctaaactgaa aactcctagt caactncaca 480

ctttattccc tggatcctca attgggttcc catgtnccgt tagtgtttct tggtaagnct 540

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ctgccancac cgnaggatcg actctaatca catctcaact gaattatggn aaagtcaact 600

caattctctc aaccatccca ggctccacta tggntaatat gctaaggaga gctgacccaa 660

cggggagaag atctgngggg gaggagagaa acaaagntaa tggaatnatt ctcgaaaagc 720

ccacaaggng aaggataacc cncttccnct cgaaagaggg gggatcgcca gatntcgcgc 780

ccggaaagaa accggggnga gggggttaca ntgtaagnc 819

<210> SEQ ID NO 119
<211> LENGTH: 796
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(796)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 119

tnttggctgg tactgcttga gcaactggtg aaactccgcg cctcacgccc cgggtgtgtc 60

cttgtccagg ggcgacgagc attctgggcg aagtccgcac gcctcttgtt cgaggcggaa 120

gacggggtct gatgctttct ccttggtcgg gactgtctcg aggcatgcat gtccagtgac 180

tcttgtgttt gctgctgctt ccctctcaga ttcttctcac cgttgtggtc agctctgctt 240

taggcatatt aatccatagt ggaggctggg atgggtgaga gaattgaggt gacttttcca 300

taattcaggt gagatgtgat tagagttcga tctgcggtgg tggcagaggc ttacaagaaa 360

cactaacggg acatgggaac caattgagga tcagggaata aagtgtgaag ttgactagga 420

ggttttcagt ttagaacatg gcagagacat tctcagaaat aaggaagtta ggaagaaaga 480

ctggtttaga gaggagggcg angaagtggt ttgggaagtg tcactttggg aagtgccagc 540

aggtgaaaat gcctgtgaca ggatggagct gaaaacagga tcaattccat agattccagt 600

tgatgtngga gcaggggaga agtcttagct aaggaagggg aagaggaggc caaggnaaca 660

cttaggacaa ttgnaacgan gggggggggag aagagnaagg gccacttagg ggaataatnt 720

ggtgggggac ccccaagnna gggcgcannn ttaggagggg gggannntcan aggaaagtgg 780

aagnttgggt ttanct 796

<210> SEQ ID NO 120
<211> LENGTH: 802
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(802)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 120

attcgtcgta ncccgatnac tatagggcga cttggagctc caccgcggtg gcggncgcgg 60

gcagggnccg gncctttgtg gccgcccggg ccgcgaagcc ggtgtcctaa aagatgaggg 120

gcggggcgcg gncggttggg gctggggaac cccgtgtggg aaaccaggag gggcggcccg 180

tttctcgggc ttcgggcgcg gccgggtgga gagagattcc ggggagcctt ggtccggaaa 240

tgctgtttgc tcgaagacgt ctcagggcgc aggtgccttg ggccgggatt agtagccgtc 300

tgaactggag tggagtagga gaaagaggaa gcgtcttggg ctgggtctgc ttgagcaact 360

ggtgaaactc cgcgcctcac gccccgggtg tgtccttgtc caggggcgac gagcattctg 420

ggcgaagtcc gcacgcctct tgttcgaggc ggaagacggg gtcttgatgc tttctccttg 480

-continued

ggtcggggac tgtctcgagg catgcatgtc cagtgactct tgtgtttggt gntgcttccc 540

tctcagatct tctcaccgng gtgggcaact ctgtttaggc atattatcca tagnggaggc 600

tggatggttg aaanaattga ggtnattttc cataatcaag tgaaatttga tagagtccgn 660

ctttnggggt gnaagggtta aaaaaaaata acggaaatgg aacaatgagg tcaaggatta 720

gttgagttgn tagnggttca attaganatg aaggnatcta aaataggagt agagaannng 780

ttnaaagagg gaaaattttg cc 802

<210> SEQ ID NO 121
<211> LENGTH: 793
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(793)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 121

atatgcagcc gcgtaattaa cctcactaaa gggaacaaaa gctgggtacc gggcccccccc 60

tcgaggtcga cggtatcgat aagcttgata tcgaattcct gcagcccggg ggatccgccc 120

cgcggcctcc caaagtgctg ggattacagg cgtgagccac cgccccgggn ctcacatttt 180

atttctattg gctagcgctg ctctaaatct tctgttcctt ctgctacacc aggcctaaca 240

ctcaaaatcc ctgccaacct tttccttcct gaagcttccc tccccttcct cagctctggc 300

gaccctgcgc tgtggtggtt ctccaaccac actcattctc ctcagctggc tccttgctct 360

tcttccaccc cctcgntgga agtgttccta agtgtttggc ttggcctcct cttccccttc 420

cttagcttag acttctccac tgctccaaca tcaactggaa atctatggaa ttgattcctg 480

tttcagctcc agtcctgttc acaggggatt ttcanctggt ggcatttcca aagtgaaatt 540

ccaaaccact tcctcggcct cctcttctaa ancaggtctt tcttcctaac ttccttattc 600

ttgagaatgt ctctgcatgt tcttaaantg aaaactccta gtcaaattca aatttatccc 660

tgatcccaaa tggtcccatt cccgtagggt ttntgtagcc tgcacaccga ggtcggantt 720

tatnnattca ccgattatgg aaagtaacca atcttnacca nccagctcat ttgttntntg 780

ctaagagggt ncc 793

<210> SEQ ID NO 122
<211> LENGTH: 440
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(440)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 122

aaagtcatgg attcctttag gtagctacat tatcaacctt tttgagaata aaatgaattg 60

agagtgttac agtctaattc tatatcacat gtaactttta tttggatata tcagtaatag 120

tgctttttcn ttttttttt ttnttttttt tnnttttngg gganagagtc tcgctctgtc 180

gccaggttgg agtgcaatgg tgcgatcttg gctcactgaa agctccaccn cccgggttca 240

agtgattctc ctgcctcagc cncccaagta gntgggacta caggggtgcg ccaccacgcc 300

tgggataatt ttgggntttt tagtagagat ggcgtttcac cancttggng caggctggtc 360

-continued

ttggaactcc tganatcatg atctgcctgc cttagcctcc ccaaagtgct gggattncag 420

gggtgagcca ctgttcctgg 440

<210> SEQ ID NO 123
<211> LENGTH: 453
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(453)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 123

cttagtctgt ntcgtagtca tattaattgt aagtntacac taataagaat gtgtcagagc 60

tcttaatgtc aaaactttga ttacacagtc cctttaaggc agttctgttt taaccccagg 120

tgggttaaat attccagcta tctgaggagc ttttngataa ttggacctca ccttagtagt 180

tctctaccct ggccacacat tagaatcact tgggagcttt taaaactgta agctctgccc 240

tgagatattc ttactcaatt taattgtgta gtttttaaaa ttccccagga aattctggta 300

tttctgttta ggaaccgctg cctcaagcct agcagnacag atatgtagga aattagctct 360

gtaaggttgg tcttacaggg gataaacaga tccttcctta gnccctggga cttaatcact 420

gagagtttgg gtggnggttt ngnatttaat gac 453

<210> SEQ ID NO 124
<211> LENGTH: 369
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(369)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 124

gacacacatt cacacataat tatgaaagca ttttcaggca aaactcaatc acaagtctgg 60

gtttttaaca tagttaactg aatatttccc ttgggggggtt aaattttaga acagacgtnc 120

atncaatctg gaagaagagc tatgaaaaaa acctagcttg ggtnggtttc atagggtnca 180

ttatgnacac attgttattt tatcccttaa tnctagtaaa gaaatagaat ctgaaaataa 240

gtaaaactac ttggaaaaaa nttaaaagat acagaaattt ctatcttaaa tgatgtgtgg 300

gccnctgtga ttttagtngg gntggttaaa ancccagagg tgaagagnat nctctatgct 360

gtgnggggg 369

<210> SEQ ID NO 125
<211> LENGTH: 516
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(516)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 125

gctcatcatg cttcacgggg gaggctgtgc gggaagaatg ctcccacaca gnataaagaa 60

tgctcccgca caggatagag aatgcccccg cacagcatag agaagccccc gcacagcata 120

gagaatgccc ccncacagca tagagaagcc cccgcacagc atagagaatg ctcttcacct 180

-continued

ctgggttttt aaccagccaa actaaaatca cagaggscma cacatcattt aagatagaaa 240

tttctgtatc ttttaattty tttcmaagta gttttactta ttttcagatt ctatttcttt 300

actagaatta agggataaaa taacaatgtg tgcataatga accctatgaa acmaacmmaa 360

gctaggtttt tttcatagst cttcttccag attgaatgaa cgtctgttct aaaatttaac 420

cccccaggga aatattcagt taactatgtt aaaaacccag acttgtgatt gagttttgcc 480

tgaaaatgct ttcataatta tgtgtgaatg tgtgtc 516

<210> SEQ ID NO 126
<211> LENGTH: 121
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 126

gtataatgca ggtgctataa ggtgagcatg agacacagat ctttgctttc caccctgttc 60

ttcttatggt tgggtattct tgtcacagta acttaactga tctaggaaag aaaaaatgtt 120

t 121

<210> SEQ ID NO 127
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 127

tggagactgg aacacaac 18

<210> SEQ ID NO 128
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide primer

<400> SEQUENCE: 128

gtgtggccag ggtagagaac t 21

<210> SEQ ID NO 129
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide primer

<400> SEQUENCE: 129

atctccggca ggcatatct 19

<210> SEQ ID NO 130
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: PCR primer

<400> SEQUENCE: 130

tgaaatcaca gccaagatga g 21

<210> SEQ ID NO 131
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 131

ccatagcctg tttcgtagc 19

<210> SEQ ID NO 132
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 132

ccatagccta tttcgtagc 19

<210> SEQ ID NO 133
<211> LENGTH: 2792
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 133

tgggacaggc agctccgggg tccgcggttt cacatcggaa acaaaacagc ggctggtctg 60

gaaggaacct gagctacgag ccgcggcggc agcggggcgg cggggaagcg tatacctaat 120

ctgggagcct gcaagtgaca acagcctttg cggtccttag acagcttggc ctggaggaga 180

acacatgaaa gaaagaacct caagaggctt tgttttctgt gaaacagtat ttctatacag 240

ttgctccaat gacagagtta cctgcaccgt tgtcctactt ccagaatgca cagatgtctg 300

aggacaacca cctgagcaat actgtacgta gccagaatga caatagagaa cggcaggagc 360

acaacgacag acggagcctt ggccaccctg agccattatc taatggacga ccccagggta 420

actcccggca ggtggtggag caagatgagg aagaagatga ggagctgaca ttgaaatatg 480

gcgccaagca tgtgatcatg ctctttgtcc ctgtgactct ctgcatggtg gtggtcgtgg 540

ctaccattaa gtcagtcagc ttttataccc ggaaggatgg gcagctaatc tatacccccat 600

tcacagaaga taccgagact gtgggccaga gagccctgca ctcaattctg aatgctgcca 660

tcatgatcag tgtcattgtt gtcatgacta tcctcctggt ggttctgtat aaatacaggt 720

gctataaggt catccatgcc tggcttatta tatcatctct attgttgctg ttctttttt 780

cattcattta cttgggggaa gtgtttaaaa cctataacgt tgctgtggac tacattactg 840

ttgcactcct gatctggaat tttggtgtgg tgggaatgat ttccattcac tggaaaggtc 900

cacttcgact ccagcaggca tatctcatta tgattagtgc cctcatggcc ctggtgttta 960

tcaagtacct ccctgaatgg actgcgtggc tcatcttggc tgtgatttca gtatatgatt 1020

tagtggctgt tttgtgtccg aaaggtccac ttcgtatgct ggttgaaaca gctcaggaga 1080

gaaatgaaac gctttttcca gctctcattt actcctcaac aatggtgtgg ttggtgaata 1140

tggcagaagg agacccggaa gctcaaagga gagtatccaa aaattccaag tataatgcag 1200

aaagcacaga aagggagtca caagacactg ttgcagagaa tgatgatggc gggttcagtg 1260

aggaatggga agcccagagg gacagtcatc tagggcctca tcgctctaca cctgagtcac 1320

gagctgctgt ccaggaactt tccagcagta tcctcgctgg tgaagaccca gaggaaaggg 1380

gagtaaaact tggattggga gatttcattt tctacagtgt tctggttggt aaagcctcag 1440

caacagccag tggagactgg aacacaacca tagcctgttt cgtagccata ttaattggtt 1500

tgtgccttac attattactc cttgccattt tcaagaaagc attgccagct cttccaatct 1560

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ccatcacctt tgggcttgtt ttctactttg ccacagatta tcttgtacag ccttttatgg 1620

accaattagc attccatcaa ttttatatct agcatatttg cggttagaat cccatggatg 1680

tttcttcttt gactataacc aaatctgggg aggacaaagg tgattttcct gtgtccacat 1740

ctaacaaagt caagattccc ggctggactt ttgcagcttc cttccaagtc ttcctgacca 1800

ccttgcacta ttggactttg gaaggaggtg cctatagaaa acgattttga acatacttca 1860

tcgcagtgga ctgtgtccct cggtgcagaa actaccagat ttgagggacg aggtcaagga 1920

gatatgatag gcccggaagt tgctgtgccc catcagcagc ttgacgcgtg gtcacaggac 1980

gatttcactg acactgcgaa ctctcaggac taccggttac caagaggtta ggtgaagtgg 2040

tttaaaccaa acggaactct tcatcttaaa ctacacgttg aaaatcaacc caataattct 2100

gtattaactg aattctgaac ttttcaggag gtactgtgag gaagagcagg caccagcagc 2160

agaatgggga atggagaggt gggcaggggt tccagcttcc ctttgatttt ttgctgcaga 2220

ctcatccttt ttaaatgaga cttgttttcc cctctctttg agtcaagtca aatatgtaga 2280

ttgcctttgg caattcttct tctcaagcac tgacactcat taccgtctgt gattgccatt 2340

tcttcccaag gccagtctga acctgaggtt gctttatcct aaaagtttta acctcaggtt 2400

ccaaattcag taaattttgg aaacagtaca gctatttctc atcaattctc tatcatgttg 2460

aagtcaaatt tggattttcc accaaattct gaatttgtag acatacttgt acgctcactt 2520

gcccccagat gcctcctctg tcctcattct tctctcccac acaagcagtc tttttctaca 2580

gccagtaagg cagctctgtc rtggtagcag atggtcccat tattctaggg tcttactctt 2640

tgtatgatga aaagaatgtg ttatgaatcg gtgctgtcag ccctgctgtc agaccttctt 2700

ccacagcaaa tgagatgtat gcccaaagcg gtagaattaa agaagagtaa aatggctgtt 2760

gaagcaaaaa aaaaaaaaaa aaaaaaaaaa aa 2792

<210> SEQ ID NO 134
<211> LENGTH: 467
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 134

Met Thr Glu Leu Pro Ala Pro Leu Ser Tyr Phe Gln Asn Ala Gln Met
1 5 10 15
Ser Glu Asp Asn His Leu Ser Asn Thr Val Arg Ser Gln Asn Asp Asn
20 25 30
Arg Glu Arg Gln Glu His Asn Asp Arg Arg Ser Leu Gly His Pro Glu
35 40 45
Pro Leu Ser Asn Gly Arg Pro Gln Gly Asn Ser Arg Gln Val Val Glu
50 55 60
Gln Asp Glu Glu Glu Asp Glu Glu Leu Thr Leu Lys Tyr Gly Ala Lys
65 70 75 80
His Val Ile Met Leu Phe Val Pro Val Thr Leu Cys Met Val Val Val
85 90 95
Val Ala Thr Ile Lys Ser Val Ser Phe Tyr Thr Arg Lys Asp Gly Gln
100 105 110
Leu Ile Tyr Thr Pro Phe Thr Glu Asp Thr Glu Thr Val Gly Gln Arg
115 120 125
Ala Leu His Ser Ile Leu Asn Ala Ala Ile Met Ile Ser Val Ile Val
130 135 140
Val Met Thr Ile Leu Leu Val Val Leu Tyr Lys Tyr Arg Cys Tyr Lys
145 150 155 160
Val Ile His Ala Trp Leu Ile Ile Ser Ser Leu Leu Leu Leu Phe Phe
165 170 175
Phe Ser Phe Ile Tyr Leu Gly Glu Val Phe Lys Thr Tyr Asn Val Ala
180 185 190
Val Asp Tyr Ile Thr Val Ala Leu Leu Ile Trp Asn Phe Gly Val Val
195 200 205
Gly Met Ile Ser Ile His Trp Lys Gly Pro Leu Arg Leu Gln Gln Ala
210 215 220
Tyr Leu Ile Met Ile Ser Ala Leu Met Ala Leu Val Phe Ile Lys Tyr

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```
225                 230                 235                 240
Leu Pro Glu Trp Thr Ala Trp Leu Ile Leu Ala Val Ile Ser Val Tyr
                245                 250                 255
Asp Leu Val Ala Val Leu Cys Pro Lys Gly Pro Leu Arg Met Leu Val
            260                 265                 270
Glu Thr Ala Gln Glu Arg Asn Glu Thr Leu Phe Pro Ala Leu Ile Tyr
        275                 280                 285
Ser Ser Thr Met Val Trp Leu Val Asn Met Ala Glu Gly Asp Pro Glu
    290                 295                 300
Ala Gln Arg Arg Val Ser Lys Asn Ser Lys Tyr Asn Ala Glu Ser Thr
305                 310                 315                 320
Glu Arg Glu Ser Gln Asp Thr Val Ala Glu Asn Asp Asp Gly Gly Phe
                325                 330                 335
Ser Glu Glu Trp Glu Ala Gln Arg Asp Ser His Leu Gly Pro His Arg
            340                 345                 350
Ser Thr Pro Glu Ser Arg Ala Ala Val Gln Glu Leu Ser Ser Ser Ile
        355                 360                 365
Leu Ala Gly Glu Asp Pro Glu Glu Arg Gly Val Lys Leu Gly Leu Gly
    370                 375                 380
Asp Phe Ile Phe Tyr Ser Val Leu Val Gly Lys Ala Ser Ala Thr Ala
385                 390                 395                 400
Ser Gly Asp Trp Asn Thr Thr Ile Ala Cys Phe Val Ala Ile Leu Ile
                405                 410                 415
Gly Leu Cys Leu Thr Leu Leu Leu Leu Ala Ile Phe Lys Lys Ala Leu
            420                 425                 430
Pro Ala Leu Pro Ile Ser Ile Thr Phe Gly Leu Val Phe Tyr Phe Ala
        435                 440                 445
Thr Asp Tyr Leu Val Gln Pro Phe Met Asp Gln Leu Ala Phe His Gln
    450                 455                 460
Phe Tyr Ile
465
```

<210> SEQ ID NO 135
<211> LENGTH: 1964
<212> TYPE: DNA
<213> ORGANISM: Mus musculus
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1964)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 135

```
accanacanc ggcagctgag gcggaaacct aggctgcgag ccggccgccc gggcgcggag     60

agagaaggaa ccaacacaag acagcagccc ttcgaggtct ttaggcagct tggaggagaa    120

cacatgagag aaagaatccc aagaggtttt gttttctttg agaaggtatt tctgtccagc    180

tgctccaatg acagagatac ctgcaccttt gtcctacttc cagaatgccc agatgtctga    240

ggacagccac tccagcagcg ccatccggag ccagaatgac agccaagaac ggcagcagca    300

gcatgacagg cagagacttg acaaccctga gccaatatct aatgggcggc cccagagtaa    360

ctcaagacag gtggtggaac aagatgagga ggaagacgaa gagctgacat tgaaatatgg    420

agccaagcat gtcatcatgc tctttgtccc cgtgaccctc tgcatggtcg tcgtcgtggc    480

caccatcaaa tcagtcagct tctatacccg gaaggacggt cagctaatct acaccccatt    540

cacagaagac actgagactg taggccaaag agccctgcac tcgatcctga atgcggccat    600

catgatcagt gtcattgtca ttatgaccat cctcctggtg gtcctgtata aatacaggtg    660

ctacaaggtc atccacgcct ggcttattat ttcatctctg ttgttgctgt tctttttttc    720

gttcatttac ttaggggaag tatttaagac ctacaatgtc gccgtggact acgttacagt    780

agcactccta atctggaatt ttggtgtggt cgggatgatt gccatccact ggaaaggccc    840

ccttcgactg cagcaggcgt atctcattat gatcagtgcc ctcatggccc tggtatttat    900

caagtacctc cccgaatgga ccgcatggct catcttggct gtgatttcag tatatgattt    960

ggtggctgtt ttatgtccca aaggcccact tcgtatgctg gttgaaacag ctcaggaaag   1020
```

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```
aaatgagact ctctttccag ctcttatcta ttcctcaaca atggtgtggt tggtgaatat   1080

ggctgaagga gacccagaag cccaaaggag ggtacccaag aaccccaagt ataacacaca   1140

aagagcggag agagagacac aggacagtgg ttctgggaac gatgatggtg gcttcagtga   1200

ggagtgggag gcccaaagag acagtcacct ggggcctcat cgctccactc ccgagtcaag   1260

agctgctgtc caggaacttt ctgggagcat tctaacgagt gaagacccgg aggaaagagg   1320

agtaaaactt ggactgggag atttcatttt ctacagtgtt ctggttggta aggcctcagc   1380

aaccgccagt ggagactgga acacaaccat agcctgcttt gtagccatac tgatcggcct   1440

gtgccttaca ttactcctgc tcgccatttt caagaaagcg ttgccagccc tccccatctc   1500

catcaccttc gggctcgtgt tctacttcgc cacggattac cttgtgcagc ccttcatgga   1560

ccaacttgca ttccatcagt tttatatcta gcctttctgc agttagaaca tggatgtttc   1620

ttctttgatt atcaaaaaca caaaaacaga gagcaagccc gaggaggaga ctggtgactt   1680

tcctgtgtcc tcagctaaca aaggcaggac tccagctgga cttctgcagc ttccttccga   1740

gtctccctag ccacccgcac tactggactg tggaaggaag cgtctacaga ggaacggttt   1800

ccaacatcca tcgctgcagc agacggtgtc cctcagtgac ttgagagaca aggacaagga   1860

aatgtgctgg gccaaggagc tgccgtgctc tgctagcttt gaccgtgggc atggagattt   1920

acccgcactg tgaactctct aaggtaaaca aagtgaggtg aacc                     1964
```

<210> SEQ ID NO 136
<211> LENGTH: 467
<212> TYPE: PRT
<213> ORGANISM: Mus musculus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(467)
<223> OTHER INFORMATION: where X is unknown or other

<400> SEQUENCE: 136

```
Met Thr Glu Ile Pro Ala Pro Leu Ser Tyr Phe Gln Asn Ala Gln Met
1               5                  10                  15
Ser Glu Asp Ser His Ser Ser Ser Ala Ile Arg Ser Gln Asn Asp Ser
            20                  25                  30
Gln Glu Arg Gln Gln Gln His Asp Arg Gln Arg Leu Asp Asn Pro Glu
        35                  40                  45
Pro Ile Ser Asn Gly Arg Pro Gln Ser Asn Ser Arg Gln Val Val Glu
    50                  55                  60
Gln Asp Glu Glu Glu Asp Glu Glu Leu Thr Leu Lys Tyr Gly Ala Lys
65                  70                  75                  80
His Val Ile Met Leu Phe Val Pro Val Thr Leu Cys Met Val Val Val
                85                  90                  95
Val Ala Thr Ile Lys Ser Val Ser Phe Tyr Thr Arg Lys Asp Gly Gln
            100                 105                 110
Leu Ile Tyr Thr Pro Phe Thr Glu Asp Thr Glu Thr Val Gly Gln Arg
        115                 120                 125
Ala Leu His Ser Ile Leu Asn Ala Ala Ile Met Ile Ser Val Ile Val
    130                 135                 140
Ile Met Thr Ile Leu Leu Val Val Leu Tyr Lys Tyr Arg Cys Tyr Lys
145                 150                 155                 160
Val Ile His Ala Trp Leu Ile Ile Ser Ser Leu Leu Leu Leu Phe Phe
                165                 170                 175
Phe Ser Phe Ile Tyr Leu Gly Glu Val Phe Lys Thr Tyr Asn Val Xaa
            180                 185                 190
Val Asp Tyr Val Thr Val Ala Leu Leu Ile Trp Asn Trp Gly Val Val
        195                 200                 205
Gly Met Ile Ala Ile His Trp Lys Gly Pro Leu Arg Leu Gln Gln Ala
    210                 215                 220
Tyr Leu Ile Met Ile Ser Ala Leu Met Ala Leu Val Phe Ile Lys Tyr
225                 230                 235                 240
Leu Pro Glu Trp Thr Ala Trp Leu Ile Leu Ala Val Ile Ser Val Tyr
                245                 250                 255
Asp Leu Val Ala Val Leu Cys Pro Lys Gly Pro Leu Arg Met Leu Val
            260                 265                 270
Glu Thr Ala Gln Glu Arg Asn Glu Thr Leu Phe Pro Ala Leu Ile Tyr
```

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```
        275                 280                 285
Ser Ser Thr Met Val Trp Leu Val Asn Met Ala Glu Gly Asp Pro Glu
    290                 295                 300
Ala Gln Arg Arg Val Pro Lys Asn Pro Lys Tyr Asn Thr Gln Arg Ala
305                 310                 315                 320
Glu Arg Glu Thr Gln Asp Ser Gly Ser Gly Asn Asp Asp Gly Gly Phe
                325                 330                 335
Ser Glu Glu Trp Glu Ala Gln Arg Asp Ser His Leu Gly Pro His Arg
            340                 345                 350
Ser Thr Pro Glu Ser Arg Ala Ala Val Gln Glu Leu Ser Gly Ser Ile
        355                 360                 365
Leu Thr Ser Glu Asp Pro Glu Glu Arg Gly Val Lys Leu Gly Leu Gly
    370                 375                 380
Asp Phe Ile Phe Tyr Ser Val Leu Val Gly Lys Ala Ser Ala Thr Ala
385                 390                 395                 400
Ser Gly Asp Trp Asn Thr Thr Ile Ala Cys Xaa Val Ala Ile Leu Ile
                405                 410                 415
Gly Leu Cys Leu Xaa Leu Leu Leu Leu Ala Ile Tyr Lys Lys Gly Xaa
            420                 425                 430
Pro Ala Xaa Pro Ile Ser Ile Thr Phe Gly Phe Val Phe Xaa Phe Ala
        435                 440                 445
Thr Asp Tyr Leu Val Gln Pro Phe Met Asp Gln Leu Ala Phe His Gln
    450                 455                 460
Phe Tyr Ile
465
```

<210> SEQ ID NO 137
<211> LENGTH: 2285
<212> TYPE: DNA
<213> ORGANISM: Mus musculus
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(2285)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 137

```
gaattcggca cgagggcatt tccagcagtg aggagacagc cagaagcaag cttttggagc     60

tgaaggaacc tgagacagaa gctagtcccc cctctgaatt ttactgatga agaaactgag    120

gccacagagc taaagtgact tttcccaagg tcgcccagcg aggacgtggg acttctcaga    180

cgtcaggaga gtgatgtgag ggagctgtgt gaccatagaa agtgacgtgt taaaaaccag    240

cgctgccctc tttgaaagcc agggagcatc attcatttag cctgctgaga agaagaaacc    300

aagtgtccgg gattcaagac ctctctgcgg ccccaagtgt tcgtggtgct tccagaggca    360

gggctatgct cacattcatg gcctctgaca gcgaggaaga agtgtgtgat gagcggacgt    420

ccctaatgtc ggccgagagc cccacgccgc gctcctgcca ggagggcagg cagggcccag    480

aggatggaga gaatactgcc cagtggagaa gccaggagaa cgaggaggac ggtgaggagg    540

accctgaccg ctatgtctgt agtggggttc ccgggcggcc gccaggcctg gaggaagagc    600

tgaccctcaa atacggagcg aagcatgtga tcatgctgtt tgtgcctgtc actctgtgca    660

tgatcgtggt ggtagccacc atcaagtctg tgcgcttcta cacagagaag aatggacagc    720

tcatctacac gccattcact gaggacacac cctcggtggg ccagcgcctc ctcaactccg    780

tgctgaacac cctcatcatg atcagcgtca tcgtggttat gaccatcttc ttggtggtgc    840

tctacaagta ccgctgctac aagttcatcc atggctggtt gatcatgtct tcactgatgc    900

tgctgttcct cttcacctat atctaccttg gggaagtgct caagacctac aatgtggcca    960

tggactaccc caccctcttg ctgactgtct ggaacttcgg ggcagtgggc atggtgtgca   1020

tccactggaa gggccctctg gtgctgcagc aggcctacct catcatgatc agtgcgctca   1080

tggccctagt gttcatcaag tacctcccag agtggtccgc gtgggtcatc ctgggcgcca   1140

tctctgtgta tgatctcgtg gctgtgctgt gtcccaaagg gcctctgaga atgctggtag   1200
```

-continued

```
aaactgccca ggagagaaat gagcccatat tccctgccct gatatactca tctgccatgg   1260

tgtggacggt tggcatggcg aagctggacc cctcctctca gggtgccctc cagctccct   1320

acgacccgga gatggaagaa gactcctatg acagttttgg ggagccttca taccccgaag   1380

tctttgagcc tcccttgact ggctacccag gggaggagct ggaggaagag gaggaaaggg   1440

gcgtgaagct tggcctcggg gacttcatct tctacagtgt gctggtgggc aaggcggctg   1500

ccacgggcag cggggactgg aataccacgc tggcctgctt cgtggccatc ctcattggct   1560

tgtgtctgac cctcctgctg cttgctgtgt tcaagaaggc gctgcccgcc ctccccatct   1620

ccatcacgtt cgggctcatc ttttacttct ccacggacaa cctggtgcgg ccgttcatgg   1680

acaccctggc ctcccatcag ctctacatct gagggacatg gtgtgccaca ggctgcaagc   1740

tgcagggaat tttcattgga tgcagttgta tagttttaca ctctagtgcc atatattttt   1800

aagacttttc tttccttaaa aaataaagta cgtgtttact tggtgaggag gaggcagaac   1860

cagctctttg gtgccagctg tttcatcacc agactttggc tcccgctttg gggagcgcct   1920

cgcttcacgg acaggaagca cagcaggttt atccagatga actgagaagg tcagattagg   1980

gtggggagaa gagcatccgg catgagggct gagatgccca aagagtgtgc tcgggagtgg   2040

cccctggcac ctgggtgctc tggctggaga ggaaaagcca gttccctacg aggagtgttc   2100

ccaatgcttt gtccatgatg tccttgttat tttattnccy ttanaaactg antcctnttn   2160

ttnttdcggc agtcacmctn ctgggragtg gcttaatagt aanatcaata aanagntgag   2220

tcctnttaga aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa   2280

aaaaa                                                               2285
```

<210> SEQ ID NO 138
<211> LENGTH: 448
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 138

```
Met Leu Thr Phe Met Ala Ser Asp Ser Glu Glu Glu Val Cys Asp Glu
1               5                  10                  15
Arg Thr Ser Leu Met Ser Ala Glu Ser Pro Thr Pro Arg Ser Cys Gln
            20                  25                  30
Glu Gly Arg Gln Gly Pro Glu Asp Gly Glu Asn Thr Ala Gln Trp Arg
        35                  40                  45
Ser Gln Glu Asn Glu Glu Asp Gly Glu Glu Asp Pro Asp Arg Tyr Val
    50                  55                  60
Cys Ser Gly Val Pro Gly Arg Pro Pro Gly Leu Glu Glu Glu Leu Thr
65                  70                  75                  80
Leu Lys Tyr Gly Ala Lys His Val Ile Met Leu Phe Val Pro Val Thr
                85                  90                  95
Leu Cys Met Ile Val Val Val Ala Thr Ile Lys Ser Val Arg Phe Tyr
            100                 105                 110
Thr Glu Lys Asn Gly Gln Leu Ile Tyr Thr Pro Phe Thr Glu Asp Thr
        115                 120                 125
Pro Ser Val Gly Gln Arg Leu Leu Asn Ser Val Leu Asn Thr Leu Ile
    130                 135                 140
Met Ile Ser Val Ile Val Val Met Thr Ile Phe Leu Val Val Leu Tyr
145                 150                 155                 160
Lys Tyr Arg Cys Tyr Lys Phe Ile His Gly Trp Leu Ile Met Ser Ser
                165                 170                 175
Leu Met Leu Leu Phe Leu Phe Thr Tyr Ile Tyr Leu Gly Glu Val Leu
            180                 185                 190
Lys Thr Tyr Asn Val Ala Met Asp Tyr Pro Thr Leu Leu Leu Thr Val
        195                 200                 205
Trp Asn Phe Gly Ala Val Gly Met Val Cys Ile His Trp Lys Gly Pro
    210                 215                 220
Leu Val Leu Gln Gln Ala Tyr Leu Ile Met Ile Ser Ala Leu Met Ala
225                 230                 235                 240
Leu Val Phe Ile Lys Tyr Leu Pro Glu Trp Ser Ala Trp Val Ile Leu
                245                 250                 255
Gly Ala Ile Ser Val Tyr Asp Leu Val Ala Val Leu Cys Pro Lys Gly
```

-continued

```
            260                 265                 270
Pro Leu Arg Met Leu Val Glu Thr Ala Gln Glu Arg Asn Glu Pro Ile
        275                 280                 285
Phe Pro Ala Leu Ile Tyr Ser Ser Ala Met Val Trp Thr Val Gly Met
    290                 295                 300
Ala Lys Leu Asp Pro Ser Ser Gln Gly Ala Leu Gln Leu Pro Tyr Asp
305                 310                 315                 320
Pro Glu Met Glu Glu Asp Ser Tyr Asp Ser Phe Gly Glu Pro Ser Tyr
                325                 330                 335
Pro Glu Val Phe Glu Pro Pro Leu Thr Gly Tyr Pro Gly Glu Glu Leu
            340                 345                 350
Glu Glu Glu Glu Glu Arg Gly Val Lys Leu Gly Leu Gly Asp Phe Ile
        355                 360                 365
Phe Tyr Ser Val Leu Val Gly Lys Ala Ala Ala Thr Gly Ser Gly Asp
    370                 375                 380
Trp Asn Thr Thr Leu Ala Cys Phe Val Ala Ile Leu Ile Gly Leu Cys
385                 390                 395                 400
Leu Thr Leu Leu Leu Leu Ala Val Phe Lys Lys Ala Leu Pro Ala Leu
                405                 410                 415
Pro Ile Ser Ile Thr Phe Gly Leu Ile Phe Tyr Phe Ser Thr Asp Asn
            420                 425                 430
Leu Val Arg Pro Phe Met Asp Thr Leu Ala Ser His Gln Leu Tyr Ile
        435                 440                 445
```

<210> SEQ ID NO 139
<211> LENGTH: 31
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide primer

<400> SEQUENCE: 139

ggtaccgcca ccatgacaga ggtacctgca c 31

<210> SEQ ID NO 140
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide primer

<400> SEQUENCE: 140

gaattcactg gctgtagaaa aagac 25

<210> SEQ ID NO 141
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide primer

<400> SEQUENCE: 141

ggatccggtc cacttcgtat gctg 24

<210> SEQ ID NO 142
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide primer

<400> SEQUENCE: 142

ttttttgaat tcttaggcta tggttgtgtt cca 33

<210> SEQ ID NO 143
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

-continued

<400> SEQUENCE: 143

gattagtggt tgttttgtg 19

<210> SEQ ID NO 144
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 144

gattagtggc tgttttgtg 19

<210> SEQ ID NO 145
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 145

tttttccagc tctcattta 19

<210> SEQ ID NO 146
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 146

tttttccagt tctcattta 19

<210> SEQ ID NO 147
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 147

tacagtgttc tggttggta 19

<210> SEQ ID NO 148
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 148

tacagtgttc tggttggta 19

<210> SEQ ID NO 149
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 149

tacagtgttg tggttggta 19

<210> SEQ ID NO 150

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<211> LENGTH: 1092
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1092)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 150

gtctagataa gncaacattc aggggtagaa ggggactgtt tatttttttcc tttagtctct 60

cttaaagagt gagaaaaatt ttcccaggaa tcccggtgga ctttgcttca ccactcatag 120

gttcatacca agttacaacc ccacaacctt agagcttttg ttaggaagag gcttggtggg 180

attaccgtgc ttggcttggc ttggtcagga ttcaccacca gagtcatgtg ggaggggggtg 240

ggaacccaaa caattcagga ttctgccctc aggaaataaa ggagaaaata gctgttggat 300

aaactaccag caggcactgc tacagcccat gctttgtggt ttaagggcca gctagttaca 360

atgacagcta gttactgttt ccatgtaatt ttcttaaagg tattaaattt ttctaaatat 420

tagagctgta acttccactt tctcttgaag gcacagwaag ggagtcacaa gacactgttg 480

cagagaatga tgatggcggg ttcagtgagg aatgggaasc ccagrgggac antcatctag 540

ggcctcatcg ctctacacct gagtcacgag ctkctntcca ggractttcc ancagtatcc 600

tcgctggtga agacccagag gaaagnatgt tcanttctcc atntttcaaa gtcatggatt 660

cctttaggta gctacattat caacctttttt gagaataaaa tgaattgaga gtgttacagt 720

ctaattctat atcacatgta acttttattt ggatatatca gtaatagtgc tttttynttt 780

ttttttttttt ttttttttttt ttttnggnga nagagtctcg ctctgtcgcc aggttggagt 840

gcaatggtgc gatcttggct cactgaaagc tccaccnccc gggttcaagt gattctcctg 900

cctcagccnc ccaagtagnt gggactacag gggtgcgcca ccacgcctgg gataattttg 960

ggnttttttag tagagatggc gtttcaccan cttggngcag gctggtcttg gaactcctga 1020

natcatgatc tgcctgcctt agcctcccca aagtgctggg attncagggg tgagccactg 1080

ttcctgggcc tc 1092

<210> SEQ ID NO 151
<211> LENGTH: 1003
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1003)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 151

ctgcagtgag ccgagatcat gctgctgtac tccagcctgg gccacagagc caaactccat 60

ctcccaaaaa aaaaaaatat taattaatat gatnaaatga tgcctatctc agaattcttg 120

taaggatttc ttagkacaag tgctgggtat aaactatana ttcratagat gncgattatt 180

acttaytatt gttattgata aataacagca gcatctacag ttaagactcc agagtcagtc 240

acatagaatc tggnactcct attgtagnaa accccnmmag aaagaaaaca cagctgaagc 300

ctaattttgt atatcattta ctgacttctc tcattcattg tggggttgag tagggcagtg 360

atatttttga attgtgaaat catancaaag agtgaccaac tttttaatat ttgtaaccttt 420

tccttttttag ggggagtaaa acttggattg ggagatttca ttttctacag tgttctggtt 480

ggtaaagcct cagcaacagc cagtggagac tggaacacaa ccatagcctg tttcgtagcc 540

-continued

atattaattg tmmstataca ctaataagaa tgtgtcagag ctcttaatgt cmaaactttg 600

attacacagt ccctttaagg cagttctgtt ttaaccccag gtgggttaaa tattccagct 660

atctgaggag cttttngata attggacctc accttagtag ttctctaccc tggccacaca 720

ttagaatcac ttgggagctt ttaaaactgt aagctctgcc ctgagatatt cttactcaat 780

ttaattgtgt agtttttaaa attccccagg aaattctggt atttctgttt aggaaccgct 840

gcctcaagcc tagcagcaca gatatgtagg aaattagctc tgtaaggttg gtcttacagg 900

gataaacaga tccttcctta gtccctggac ttaatcactg agagtttggg tggtggtttt 960

ggatttaatg acacaacctg tagcatgcag tgttacttaa gac 1003

<210> SEQ ID NO 152
<211> LENGTH: 1726
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1726)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 152

ggatccctcc ccttttaga ccatacaagg taacttccgg acgttgccat ggcatctgta 60

aactgtcatg gtgttggcgg ggagtgtctt ttagcatgct aatgtattat aattagcgta 120

tagtgagcag tgaggataac cagaggtcac tctcctcacc atcttggttt tggtgggttt 180

tggccagctt ctttattgca accagtttta tcagcaagat ctttatgagc tgtatcttgt 240

gctgacttcc tatctcatcc cgnaactaag agtacctaac ctcctgcaaa ttgmagncca 300

gnaggtcttg gncttatttn acccagcccc tattcaarat agagtngytc ttggnccaaa 360

cgccyctgac acaaggattt taaagtctta ttaattaagg taagatagkt ccttgsatat 420

gtggtctgaa atcacagaaa gctgaatttg gaaaaaggtg cttggasctg cagccagtaa 480

acaagttttc atgcaggtgt cagtatttaa ggtacatctc aaaggataag tacaattgtg 540

tatgttggga tgaacagaga gaatggagca anccaagacc caggtaaaag agaggacctg 600

aatgccttca gtgaacaatg atagataatc tagactttta aactgcatac ttcctgtaca 660

ttgtttttc ttgcttcagg tttttagaac tcatagtgac gggtctgttg ttaatcccag 720

gtctaaccgt taccttgatt ctgctgagaa tctgatttac tgaaaatgtt tttcttgtgc 780

ttatagaatg acaatagaga acggcaggag cacaacgaca gacggagcct tggccaccct 840

ganccattat ctaatggacg acccagggta actcccggca ggtggtggan caagatgagg 900

aagaagatga gganctgaca ttgaaatatg ncgscaagca tgtgatcatg ctctttgkcc 960

ctgtgactct ctgcatggtg gtggtcgtgg ntaccattaa gtcagtcagc ttttataccc 1020

ggaaggatgg gcagctgtac gtatgagttt kgttttatta ttctcaaasc cagtgtggct 1080

tttctttaca gcatgtcatc atcaccttga aggcctctnc attgaagggg catgacttag 1140

ctggagagcc catcctctgt gatggtcagg agcagttgag agancgaggg gttattactt 1200

catgttttaa gtggagaaaa ggaacactgc agaagtatgt ttcctgtatg gtattactgg 1260

atagggctga agttatgctg aattgaacac ataaattctt ttccacctca gggncattgg 1320

gcgcccattg ntcttctgcc tagaatattc tttccttttnc tnacttkggn ggattaaatt 1380

cctgtcatcc ccctcctctt ggtgttatat ataaagtntt ggtgccgcaa aagaagtagc 1440

actcgaatat aaaattttcc ttttaattct cagcaaggna agttacttct atatagaagg 1500

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gtgcacccnt acagatggaa caatggcaag cgcacatttg ggacaaggga ggggaaaggg 1560

ttcttatccc tgacacacgt ggtcccngct gntgtgtnct ncccccactg antagggtta 1620

gactggacag gcttaaacta attccaattg gntaatttaa agagaatnat ggggtgaatg 1680

ctttgggagg agtcaaggaa gagnaggtag naggtaactt gaatga 1726

<210> SEQ ID NO 153
<211> LENGTH: 1883
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1883)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 153

cncgtataaa agaccaacat tgccancnac aaccacaggc aagatcttct cctaccttcc 60

cccnnggtgt aataccaagt attcnccaat ttgtgataaa ctttcattgg aaagtgacca 120

ccctccttgg ttaatacatt gtctgtgcct gctttcacac tacagtagca cagttgagtg 180

tttgccctgg agaccatatg acccatagag cttaaaatat tcagtctggc tttttacaga 240

gatgtttctg actttgttaa tagaaaatca acccaactgg tttaaataat gcacatactt 300

tctctctcat agagtagtgc agaggtagnc agtccagatt agtasggtgg cttcacgttc 360

atccaaggac tcaatctcct tctttcttct ttagcttcta acctctagct tacttcaggg 420

tccaggctgg agccctascc ttcatttctg acagtaggaa ggagtagggg agaaaagaac 480

ataggacatg tcagcagaat tctctcctta gaagttccat acacaacaca tctccctaga 540

agtcattgcc cttacttgtt ctcatagcca tcctaaatat aagggagtca gaagtaaagt 600

ctkkntggct gggaatattg gcacctggaa taaaaatgtt tttctgtgaa tgagaaacaa 660

ggggaagatg gatatgtgac attatcttaa gacaactcca gttgcaatta ctctgcagat 720

gagaggcact aattataagc catattacct ttcttctgac aaccacttgt cagcccncgt 780

ggtttctgtg gcagaatctg gttcyatamc aagttcctaa taanctgtas ccnaaaaaat 840

ttgatgaggt attataatta tttcaatata aagcacccac tagatggagc cagtgtctgc 900

ttcacatgtt aagtccttct ttccatatgt tagacatttt ctttgaagca attttagagt 960

gtagctgttt ttctcaggtt aaaaattctt agctaggatt ggtgagttgg ggaaaagtga 1020

cttataagat ncgaattgaa ttaagaaaaa gaaaattctg tgttggaggt ggtaatgtgg 1080

ktggtgatct ycattaacac tganctaggg ctttkgkgtt tgktttattg tagaatctat 1140

accccattca nagaagatac cgagactgtg ggccagagag ccctgcactc aattctgaat 1200

gctgccatca tgatcagngt cattgtwgtc atgactannc tcctggtggt tcwgtataaa 1260

tacaggtgct ataaggtgag catgagacac agatctttgn tttccaccct gttcttctta 1320

tggttgggta ttcttgtcac agtaacttaa ctgatctagg aaagaaaaaa tgttttgtct 1380

tctagagata agttaatttt tagttttctt cctcctcact gtggaacatt caaaaaatac 1440

aaaaaggaag ccaggtgcat gtgtaatgcc aggctcagag gctgaggcag gaggatcgct 1500

tgggcccagg agttcacaag cagcttgggc aacgtagcaa gaccctgcct ctattaaaga 1560

aaacaaaaaa caaatattgg aagtatttta tatgcatgga atctatatgt catgaaaaaa 1620

ttagtgtaaa atatatatat tatgattagn tatcaagatt tagtgataat ttatgttatt 1680

ttgggatttc aatgcctttt taggccattg tctcaamaaa taaaagcaga aaacaaaaaa 1740

-continued

agttgtaact gaaaaataaa catttccata taatagcaca atctaagtgg gtttttgntt 1800

gtttgtttgn ttgttgaagc agggccttgc cctnycaccc aggntggagt gaagtgcagt 1860

ggcacgattt tggctcactg cag 1883

<210> SEQ ID NO 154
<211> LENGTH: 1990
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1990)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 154

atgtttgaca atttctccgt tccacccttg attaaataag gtagtattca ttttttaagt 60

tttagctttt ggatatatgt gtaagtgtgg tatgctgtct aatgaattaa gacaattggt 120

nctktcttta cccmacanct ggacmaagag caggcaagat ncaanaatca agtgacccag 180

ncaaaccaga cacattttct gctctcagct agcttgccac ctagaaagac tggttgtcna 240

agttggagtc caagaatcgc ggaggatgtt taaaatgcag tttctcaggt tctcnccacc 300

caccagaagt tttgattcat tgagtggtgg gagagggcag agatatttgc gattttaaca 360

gcattctctt gattgtgatg cagctggttc scaaataggt accctaaaga aatgacaggt 420

gttaaattta ggatggccat cgcttgtatg ccgggagaag cacacgctgg gcccaattta 480

tataggggct ttcgtcctca gctcgagcar cctcagaacc ccgacaaccy acgccagckc 540

tctgggcgga ttccrtcagk tggggaagsc caggtggagc tctggkttct ccccgcaatc 600

gtttctccag gccggaggcc ccgccccctt cctcctggct cctcccctcc tccgtgggcc 660

gnccgccaac gacgccagag ccggaaatga cgacaacggt gagggttctc gggcggggcc 720

tgggacaggc agctccgggg tccncgnnwt nacatcggaa acaaaacagc ggctggtctg 780

gaaggaacct gakctacgac ccgcggcggc agcggggcgg cggggaagcg tatgtgcgtg 840

atggggagtc cgggcaagcc aggaaggcac cgcggacatg ggcggccgcg ggcagggncc 900

ggnccctttgt ggccgcccgg gccgcgaagc cggtgtccta aaagatgagg ggcggggcgc 960

ggccggttgg ggctggggaa ccccgtgtgg gaaaccagga ggggcggccc gtttctcggg 1020

cttcgggcgc ggccgggtgg agagagattc cggggagcct tggtccggaa atgctgtttg 1080

ctcgaagacg tctcagggcg caggtgcctt gggccgggat tagtagccgt ctgaactgga 1140

gtggagtagg agaaagagga agcgtcttgg gctgggtctg cttgagcaac tggtgaaact 1200

ccgcgcctca cgccccgggt gtgtccttgt ccaggggcga cgagcattct gggcgaagtc 1260

cgcacgcctc ttgttcgagg cggaagacgg ggtcttgatg ctttctcctt ggtcgggact 1320

gtctcgaggc atgcatgtcc agtgactctt gtgtttgctg ctgcttccct ctcagattct 1380

tctcaccgtt gtggtcagct ctgctttagg catattaatc catagtggag gctgggatgg 1440

gtgagagaat tgaggtgact tttccataat tcaggtgaga tgtgattaga gtycggatcc 1500

tncggtggtg gcagaggctt accaagaaac actaacggga catgggaacc aattgaggat 1560

ccagggaata aagtgtgaag ttgactagga ggttttcagt ttaagaacat ggcagagaca 1620

ttctcagaaa taaggaagtt aggaagaaag acctggttta gagaggaggg cgaggaagtg 1680

gtttggaagt gtcactttgg aagtgccagc aggtgaaaat gccctgtgaa caggactgga 1740

gctgaaaaca ggaatcaatt ccatagattt ccagttgatg ttggagcagt ggagaagtct 1800

-continued

aanctaagga aggggaagag gaggccaagc caaacactta ggaacacttn cnacgagggg 1860

gtggaagaag agcaaggagc cagctgagga gaatgagtgt ggttggagaa ccaccacagc 1920

ncagggtcgc caganctgag gaaggggagg gaagcttatc gagkamsgwc racmkcgagt 1980

tggcagggat 1990

<210> SEQ ID NO 155
<211> LENGTH: 736
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 155

gtctttccca tcttctccac agagtttgtg ccttacatta ttactccttg ccattttcaa 60

gaaagcattg tcagctcttc caatctccat caccttggg cttgttttct actttgccac 120

agattatctt gtacagcctt ttatggacca attagcattc catcaatttt atatctagca 180

tatttgcggt tagaatccca tggatgtttc ttctttgact ataacaaaat ctggggagga 240

caaaggtgat ttcctgtgtc cacatctaac aaatcaagat ccccggctgg acttttggag 300

gttccttcca agtcttcctg accaccttgc actattggac tttggaagga ggtgcctata 360

gaaaacgatt ttgaacatac ttcatcgcag tggactgtgt cctcggtgca gaaactacca 420

gatttgaggg acgaggtcaa ggagatatga taggcccgga agttgctgtg ccccatcagc 480

agcttgacgc gtggtcacag gacgattttc actgacactg cgaactctca ggactaccgt 540

taccaagagg ttaggtgaag tggtttaaac caaacggaac tcttcatctt aaactacacg 600

ttgaaaatca acccaataat tctgtattaa ctgaattctg aacttttcag gaggtactgt 660

gaggaagagc aggcaccacc agcagaatgg ggaatggaga ggtgggcagg ggttccagct 720

tccctttgat tttttg 736

<210> SEQ ID NO 156
<211> LENGTH: 1117
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1117)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 156

ggatccgccc gccttggcct cccaaagtgc tgggattaca ggcatgagcc accgctcctg 60

gctgagtctg cgatttcttg ccagctctac ccagttgtgt catcttaagc aagtcactga 120

acttctctgg attcccttct cctnnwgtaa aataagnatg ttatctgncc nncctgcctt 180

gggcattgtg ataaggataa gatgacatta tagaatntng caaaattaaa agcgctagac 240

aaatgatttt atgaaaatat aaagattagn ttgagtttgg gccagcatag aaaaaggaat 300

gttgagaaca ttccnttaag gattactcaa gcyccccttt tgstgknwaa tcaganngtc 360

atnnamntat cntntgtggg ytgaaaatgt ttggttgtct caggcggttc ctacttattg 420

ctaaagagtc ctaccttgag cttatagtaa atttgtcagt tagttgaaag tcgtgacaaa 480

ttaatacatt cctggtttac aaattggtct tataagtatt tgattggtnt aaatgnattt 540

actaggattt aactaacaat ggatgacctg gtgaaatcct atttcagacc taatctggga 600

gcctgcaagt gacaacagcc tttgcggtcc ttagacagct tggcctggag gagaacacat 660

gaaagammgg tttgwntctg nttawtgtaa tctatgraag tgtttttwat macagtataa 720

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ttgtmtgmac aaagttctgt ttttctttcc ctttncagaa cctcaagagg ctttgttttc 780

tgtgaaacag tatttctata cagntgctcc aatgacagag tnacctgcac cgttgtccta 840

cttccagaat gcacagatgt ctgaggacaa ccacctgagc aatactgtac gtagccaggt 900

acagcgtcag tytctnaaac tgcctyygnc agactggatt cacttatcat ctcccctcac 960

ctctgagaaa tgctgagggg gstaggnagg gctttctcta cttnaccaca tttnataatt 1020

atttttgggt gaccttcagc tgatcgctgg gagggacaca gggcttnttt aacacatagg 1080

gtgttggata cagnccctcc ctaattcaca tttcanc 1117

<210> SEQ ID NO 157
<211> LENGTH: 540
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(540)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 157

ctgcagcttt cctttaaact aggaagactt gttcctatac cccagtaacg atacactgta 60

cactaagcaa atagcagtca aacccaaatg aaatttntac agatgttctg tgtcatttta 120

tnttgtttat gttgtctccc ccacccccac cagttcacct gccatttatt tcatattcat 180

tcaacgtctn nntgtgtaaa aagagacaaa aaacattaaa ctttttttcct tcgttaattc 240

ctccctacca cccatttaca agtttagccc atacatttta ttagatgtct tttatgtttt 300

tcttttncta gatttagtgg ctgtttngtg tccgaaaggt ccacttcgta tgctggttga 360

aacagctcag gagagaaatg aaacgctttt tccagctctc atttactcct gtaagtattt 420

ggagaatgat attgaattag taatcagngt agaatttatc gggaacttga aganatgtna 480

ctatggcaat ttcanggnac ttgtctcatc ttaaatgana gnatccctgg actcctgnag 540

<210> SEQ ID NO 158
<211> LENGTH: 509
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(509)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 158

ccccgtcnat gcatactttg tgtgtccagt gcttacctgg aatccngtct ttcccaacag 60

caacaatggt gtggttggtg aatatggcag aaggagaccc ggaagctcaa aggagagtat 120

ccaaaaattc caagtataat gcagaaagta ggtaactyyy nttagatamn atcttgattt 180

tncagggtca ctgttataag ctaacagtat agnaatgttt ttatcgtctt tctnkggnca 240

tagactcctn kgagaatctc ttgagaacta tgataatgcc cagtaaatac ncagataagt 300

atttaaggag tncagatact caaancccaa caatacngtc aaagcatcct aggttaagac 360

amcncccatt aaatacagaa taccagcatg gaaaggttca ggctgaggtt atgattgggt 420

ttgggttttg ggnnngtttt ttataagtca tgattttaaa aagaaaaaat aaactctctc 480

caaacatgta aaagtaagaa tctcctaaa 509

<210> SEQ ID NO 159

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<211> LENGTH: 823
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(823)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 159

caggagtgga ctaggtaaat gnaagntgtt ttaaagagag atgnggncng ggacatagtg 60

gtacacanct gtaatgctca ncactkatgg ggagtactga aggnggnsgg atcacttgng 120

ggtcnggaat ntgagancag cctgggcaan atggcgaaac cctgtctcta ctaaaaatag 180

ccanaawnwa gcctagcgtg gtggcgcrca cgcgtggttc cacctactca ggaggcntaa 240

gcacgagnan tncttgaacc caggaggcag aggntgtggt garctgagat cgtgccactg 300

cactccagtc tgggcgacma agtgagaccc tgtctccnnn aagaaaaaaa aaatctgtac 360

tttttaaggg ttgtgggacc tgttaattat attgaaatgc ttctyttcta ggtcatccat 420

gcctggctta ttatatcatc tctattgttg ctgctctttt ttacattcat ttacttgggg 480

taagttgtga aatttggggt ctgtctttca gaattaacta cctnngtgct gtgtagctat 540

catttaaagc catgtacttt gntgatgaat tactctgaag ttttaattgt ntccacatat 600

aggtcatact tggtatataa aagactagnc agtattacta attgagacat tcttctgtng 660

ctcctngctt ataataagta gaactgaaag naacttaaga ctacagttaa ttctaagcct 720

ttggggaagg attatatagc cttctagtag gaagtcttgt gcnatcagaa tgtttntaaa 780

gaaagggtnt caaggaatng tataaanacc aaaaataatt gat 823

<210> SEQ ID NO 160
<211> LENGTH: 945
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(945)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 160

gttntccnaa ccaacttagg agnttggacc tgggraagac cnacntgatc tccgggaggn 60

aaagactnca gttgagccgt gattgcaccc actttactcc aagcctgggc aaccaaaatg 120

agacactggc tccaaacaca aaaacaaaaa caaaaaaaga gtaaattaat ttanagggaa 180

gnattaaata aataatagca cagttgatat aggttatggt aaaattataa aggtgggana 240

ttaatatcta atgtttggga gccatcacat tattctaaat aatgttttgg tggaaattat 300

tgtacatctt ttaaaatctg tgtaattttt tttcagggaa gtgtttaaaa cctataacgt 360

tgctgtggac tacattactg ttncactcct gatctggaat tttggtgtgg tgggaatgat 420

ttccattcac tggaaaggtc cacttcgact ccagcaggca tatctcatta tgattagtgc 480

cctcatgncc ctgktgttta tcaagtacct ccctgaatgg actgngtggc tcatcttggc 540

tgtgatttca gtatatggta aaacccaaga ctgataattt gtttgtcaca ggaatgcccc 600

actggagtgt tttctttcct catctcttta tcttgattta gagaaaatgg taacgtgtac 660

atcccataac tcttcagtaa atcattaatt agctatagta actttttcat ttgaagattt 720

cggctgggca tggtagctca tgcctgtaat cttagcactt tgggaggctg aggcgggcag 780

atcacctaag cccagagttc aagaccagcc tgggcaacat ggcaaaacct cgtatctaca 840

-continued

gaaaatacaa aaattagccg ggcatggtgg tgcacacctg tagttccagc tacttaggag 900

gctgaggtgg gaggatcgat tgatcccagg aggtcaagnc tgcag 945

<210> SEQ ID NO 161
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 161

Tyr Pro Thr Phe
1

<210> SEQ ID NO 162
<211> LENGTH: 4
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 162

Ser Thr Pro Glu
1

<210> SEQ ID NO 163
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 163

cattcactga ggacacacc 19

<210> SEQ ID NO 164
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 164

tgtagagcac caccaaga 18

<210> SEQ ID NO 165
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 165

gcatggtgtg catccact 18

<210> SEQ ID NO 166
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 166

ggaccactct gggaggta 18

<210> SEQ ID NO 167
<211> LENGTH: 18
<212> TYPE: DNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 167

aaacttggat tgggagat 18

<210> SEQ ID NO 168
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 168

Asn Asp Asn Arg Glu Arg Gln Glu His Asn Asp Arg Arg Ser Leu
1 5 10 15

<210> SEQ ID NO 169
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 169

Lys Asp Gly Gln Leu Ile Tyr Thr Pro Phe Thr Glu Asp Thr Glu
1 5 10 15

<210> SEQ ID NO 170
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 170

Glu Ala Gln Arg Arg Val Ser Lys Asn Ser Lys Tyr Asn Ala Glu
1 5 10 15

<210> SEQ ID NO 171
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 171

Ser His Leu Gly Pro His Arg Ser Thr Pro Glu Ser Arg Ala Ala
1 5 10 15

<210> SEQ ID NO 172
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide primer

<400> SEQUENCE: 172

cagaggatgg agagaatac 19

<210> SEQ ID NO 173
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide primer

<400> SEQUENCE: 173

ggctccccaa aactgtcat 19

<210> SEQ ID NO 174
<211> LENGTH: 20

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide primer

<400> SEQUENCE: 174

gccctagtgt tcatcaagta 20

<210> SEQ ID NO 175
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide primer

<400> SEQUENCE: 175

aaagcgggag ccaaagtc 18

<210> SEQ ID NO 176
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: PCR primer

<400> SEQUENCE: 176

tcacagaaga taccgagact 20

<210> SEQ ID NO 177
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<400> SEQUENCE: 177

cccaaccata agaagaacag 20

<210> SEQ ID NO 178
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: PCR primer

<400> SEQUENCE: 178

tctgtacttt ttaagggttg tg 22

<210> SEQ ID NO 179
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 179

acttcagagt aattcatcan ca 22

<210> SEQ ID NO 180
<211> LENGTH: 19
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: PCR primer

<400> SEQUENCE: 180

gactccagca ggcatatct 19

<210> SEQ ID NO 181
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<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 181

gatgagacaa gtnccntgaa 20

<210> SEQ ID NO 182
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<212> TYPE: DNA
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<400> SEQUENCE: 182

ttagtggctg tttngtgtcc 20

<210> SEQ ID NO 183
<211> LENGTH: 20
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: PCR primer

<400> SEQUENCE: 183

cacccattta caagtttagc 20

<210> SEQ ID NO 184
<211> LENGTH: 241
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
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<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(241)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 184

cncnnnnnnn nnnnnnnatt tngtctgtgc cgcntaaata ttaattgtcc ctatacanta 60

ataagantgt gtcagagctc ttaatgtcaa aactttgatt acacagtccc tttaaggcag 120

ttctgtttta accccaggtg ggttaaatat tccagctatc tgaggagctt ttngataatt 180

ggacctcacc ttagtagttc tctaccctgg ccacacatta gaatcacttg ggagctttta 240

a 241

<210> SEQ ID NO 185
<211> LENGTH: 241

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<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(241)
<223> OTHER INFORMATION: where n may be either a or g or c or t/u, unknown or other

<400> SEQUENCE: 185

tcnnnnnnnn nccccntaaa tttctccctg ccccgnaaag gttacaaata tcaaaaagnt 60

ggtcactctt nggtatgatt tcacaattca aaactatcac tgccctactc aaccccacaa 120

tgaatgagag aagtcagtaa atgatataca aaattaggct tcagctgtgt ttnctttctt 180

tngggggtttn ctacaatagg agtnccagat tctatgtgac tgactctgga gtcttaactg 240

t 241

We claim

1. An isolated antibody that binds to a mutant mammalian Presenilin protein, wherein the mutant mammalian Presenilin protein comprises at least one mutation relative to a wild-type mammalian Presenilin, the mutation being selected from the group consisting of: M 146 L; H 163 R; A 246 E; L 286 V; and C 410 Y, wherein the wild-type mammalian Presenilin has the amino acid sequence depicted in SEQ ID NO: 2 or 134.

2. The antibody according to claim **1**, wherein the antibody is a monoclonal antibody.

3. A hybridoma that produces an antibody according to claim **2**.

4. An isolated antibody raised against a mutant mammalian Presenilin protein, wherein the mutant mammalian Presenilin protein comprises at least one mutation relative to a wild-type mammalian Presenilin, the mutation being selected from the group consisting of: M 146 L; H 163 R; A 246 E; L 286 V; and C 410 Y, wherein the wild-type mammalian Presenilin has the amino acid sequence depicted in SEQ ID NO: 2 or 134.

5. The antibody according to claim **4**, wherein the antibody is a monoclonal antibody.

6. The antibody according to claim **4**, wherein the antibody is a polyclonal antibody.

7. A hybridoma that produces an antibody according to claim **5**.

8. An isolated antibody that binds to a mutant mammalian Presenilin protein, wherein the mutant mammalian Presenilin protein comprises at least one mutation relative to a wild-type mammalian Presenilin, the mutation being selected from the group consisting of: A 260 V; A 285 V; and L 392 V, wherein the wild-type mammalian Presenilin has the amino acid sequence depicted in SEQ ID NO: 2 or 134.

9. The antibody according to claim **8**, wherein the antibody is a monoclonal antibody.

10. A hybridoma that produces an antibody according to claim **9**.

11. An isolated antibody raised against a mutant mammalian Presenilin protein, wherein the mutant mammalian Presenilin protein comprises at least one mutation relative to a wild-type mammalian Presenilin, the mutation being selected from the group consisting of: A 260 V; A 285 V; and L 392 V, wherein the wild-type mammalian Presenilin has the amino acid sequence depicted in SEQ ID NO: 2 or 134.

12. The antibody according to claim **11**, wherein the antibody is a monoclonal antibody.

13. The antibody according to claim **11**, wherein the antibody is a polyclonal antibody.

14. A hybridoma that produces an antibody according to claim **12**.

* * * * *